



# ARCHIVES OF SURGERY

## EDITORIAL BOARD

DEAN LEWIS, Baltimore

EVARTS A. GRAHAM, St. Louis

WALLACE I. TERRY, San Francisco

ALTON OCHSNER, New Orleans

WILLIAM DARRACH, New York

EDWARD STARR JUDD, Rochester, Minn.

VOLUME 30  
1935

PUBLISHERS  
AMERICAN MEDICAL ASSOCIATION  
CHICAGO, ILL.





# CONTENTS OF VOLUME 30

## JANUARY 1935. NUMBER 1

	PAGE
Therapeutic Use of the Concentrated Streptococcus Serum of the New York State Department of Health in Patients with Infections of the Ear, Nose and Throat. Adele E. Sheplar, M.D.; Martha Jane Spence, M.A., and Ward J. MacNeal, M.D., New York.....	1
Relationship of Infection to Postoperative Pulmonary Complications. W. D. Sutliff, M.D., Chicago, and Brandt F. Steele, M.D., Boston.....	14
Senile Osteomalacia: Report of a Case. Samuel Kleinberg, M.D., New York .....	30
Preoperative Irradiation of Massive Tumors of the Kidney: A Clinical and Pathologic Study. Lawrence R. Wharton, M.D., Baltimore.....	35
Hemorrhagic Villous Synovitis of the Knee Joint Due to Xanthoma: Report of a Case. David H. Kling, M.D., Los Angeles, and David Sashin, M.D., New York.....	52
Congenital Coxa Vara. Isadore Zadek, M.D., New York.....	62
Irradiation in the Treatment of Tumors of the Pituitary Gland: Report of Twenty-Three Cases. Carl W. Rand, M.D., and Raymond G. Taylor, M.D., Los Angeles.....	103
Effect of Suprarenal Denervation and Splanchnic Section on the Sugar Tolerance of Dogs. Géza de Takáts, M.D., and Florian P. Cutlibert, B.S., Chicago .....	151
Gastric Secretion: V. Achlorhydria Following Partial Gastrectomy for Ulcer; Studies with Histamine and the Transplanted Gastric Pouch. Eugene Klein, M.D., New York.....	162
Fifty-Fifth Report of Progress in Orthopedic Surgery (Concluded). John G. Kuhns, M.D.; Edwin F. Cave, M.D.; Sumner M. Roberts, M.D., and Joseph S. Barr, M.D., Boston; Joseph A. Freiberg, M.D., Cincinnati; Joseph E. Milgram, M.D., New York, and Robert I. Stirling, F.R.C.S. (Edin.), Edinburgh, Scotland.....	171

## FEBRUARY 1935. NUMBER 2

Etiology and Treatment of Clawfoot: Report of the Results in One Hundred and Two Feet Treated by Anterior Tarsal Resection. John T. Saunders, M.D., New York .....	179
Massive Intravenous Injections: An Experimental Study. Harry J. Warthen, M.D., Richmond, Va.....	199
Primary Isolated Lymphogranulomatosis of the Stomach: Report of a Case. Harry N. Comando, M.D., Newark, N.J.....	228
Congenital Absence of Penis. Robert B. Drury, M.D., and Henry H. Schwarzell, M.D., Columbus, Ohio.....	236
Effects of Local Immunization on the Development of Experimental Abscesses of the Lung. William M. Tuttle, M.D., St. Louis, and Paul R. Cannon, M.D., Chicago .....	243
Epithelioma Following Avulsion of the Scalp: Report of a Case. Edward L. Burns, M.D., St. Louis.....	266
Gastric Secretion: VI. The Action of Pilocarpine on the Secretions of a Transplanted Gastric Pouch Without Auerbach's Plexus. Eugene Klein, M.D., New York .....	277
Treatment of Fractures of Vertebral Bodies Uncomplicated by Lesions of the Cord. William A. Rogers, M.D., Boston.....	284
The Schilling Hemogram in Appendicitis. Herbert A. Carlson, M.D., and Lucretia Wilder, B.S., Minneapolis.....	325
Relation of Arteries to Roots of Nerves in Posterior Cranial Fossa in Man. James Crawford Watt, M.D., and Angus Neil McKillop, M.B., Toronto, Canada .....	336

# CONTENTS OF VOLUME 30

## FEBRUARY—Continued

	PAGE
Acute Appendicitis in Children. Caleb S. Stone Jr., M.D., Santa Barbara, Calif. ....	346
Therapeutic Use of Concentrated Streptococcus Serum of New York State Department of Health in Infected Wounds. Adele E. Sheplar, M.D.; Martha Jane Spence, M.A., and Ward J. MacNeal, M.D., New York..	357

## MARCH 1935. NUMBER 3

Significance of Anaerobic Organisms in Peritonitis Due to Liver Autolysis: A Bacteriologic Study of the Peritoneal Exudates. Harold M. Trusler, M.D.; James R. Reeves, M.D., and Hugh E. Martin, A.M., Indianapolis.	371
Development and Treatment of Peptic Ulcer: An Experimental Study. Fred R. Harper, M.D., Rochester, Minn.....	394
Lymphosarcoma: A Clinical, Pathologic and Radiotherapeutic Study, with a Report of Thirty Cases. Max Cutler, M.D., Chicago.....	405
Neurofibroma of the Ureter: Report of a Case with Operation and Recovery. A. Ravich, M.D., Brooklyn.....	442
Cholecystogastrostomy and Hepatitis: An Experimental Study. Antonio Gentile, M.D., Newport News, Va.....	449
Experimental Studies on Pulmonary Suppuration. J. J. Longacre, M.D., and Louis G. Herrmann, M.D., Cincinnati.....	476
Mesenteric Lymphadenitis Simulating Acute Appendicitis: Quantitative Study of the Size of Normal Mesenteric Lymph Nodes. Charles H. Mead, M.D., Duluth, Minn. ....	492
Clinical Use of a Plastic Pylorojejunostomy in Chronic Duodenal Ulcer. Golder L. McWhorter, M.D., Ph.D., Chicago.....	528
Staphylococcic Empyema and Pyopneumothorax: Pathogenesis, Pathology, Symptoms and Treatment. Harold Neuhoof, M.D., and Maurice Berck, M.D., New York .....	543

## APRIL 1935. NUMBER 4

Reactions of Contents of Jejunum and Experimental Production of Peptic Ulcer. Patrick P. T. Wu, M.D., Rochester, Minn.....	557
Tuberculosis of a Diaphysis: Report of a Case. George E. Bennett, M.D., and H. Alvan Jones, M.D., Baltimore.....	563
Histologic Effects of Intravenous Sclerosing Solutions on Subcutaneous Tissues. Howard R. Mahorner, M.D., and Alton Ochsner, M.D., New Orleans .....	573
Carcinoma of the Body and Tail of the Pancreas. Henry K. Ransom, M.D., Ann Arbor, Mich.....	584
Slipping of the Proximal Femoral Epiphysis: Therapeutic Results in One Hundred and One Cases. Maurice M. Pomeranz, M.D., and Marian Frauenthal Sloane, M.D., New York.....	607
Rate of Absorption of Alveolar Gases in Relation to Hyperventilation. K. E. Lemmer, M.D., and E. A. Rovenstine, M.D., Madison, Wis.....	625
Postoperative Prognosis in Cancer of the Breast: Results After from Seven to Twenty Years in a Series of Cases Studied with Reference to the Rapidity of Preoperative Growth. E. MacD. Stanton, M.D., Schenectady, N. Y. ....	629
A Bronchobiliary Fistula. R. W. French, M.D., Fall River, Mass.....	635
Changes of the Bones in the Leukemias. Lloyd F. Craver, M.D., and Murray M. Copeland, M.D., New York.....	639
Median Cleft of Lower Lip and Mandible, Cleft Sternum and Absence of Basihyoid: Report of a Case. Charles Bruce Morton, M.D., and Harvey Ernest Jordan, Ph.D., University, Va.....	647
Congenital Absence of the Sacrum. W. R. Hamsa, M.D., Iowa City.....	657

# CONTENTS OF VOLUME 30

## APRIL—Continued

PAGE

Effect of Pneumothorax and Oleothorax on the Histologic Structure of the Thyroid Gland. A. Clifford Abbott, M.D., F.R.C.S. (Edin.); Alexander M. Goodwin, M.D.; Sara Meltzer, M.D., and Earl Stephenson, M.D., Ch.M., Winnipeg, Canada .....	697
Primary Sarcoma of the Duodenum: Report of a Case. Duval Prey, M.D.; John M. Foster Jr., M.D., and Wilfred Dennis, M.D., Denver.....	675
Experimental Pulmonary Embolism Associated with Venoclysis. Mervin J. Rumold, M.D., Kansas City, Kan.....	685
Differentiation of Benign and Malignant Gastric Ulcers: Unreliability of Diagnostic Criteria. Andrew B. Rivers, M.D., and Thomas J. Dry, M.B., Rochester, Minn. ....	702
Fifty-Sixth Report of Progress in Orthopedic Surgery. John G. Kulms, M.D.; Edwin F. Cave, M.D.; Sumner M. Roberts, M.D., and Joseph S. Barr, M.D., Boston; Joseph A. Freiberg, M.D., Cincinnati; Joseph E. Milgram, M.D., New York, and Robert I. Stirling, F.R.C.S. (Edin.), Edinburgh, Scotland .....	716

## MAY 1935. NUMBER 5

Cancer of the Cheek (Buccal Mucosa): Study of Ninety-Nine Cases with Results of Treatment at the End of Five Years. Hayes E. Martin, M.D., New York, and Otto H. Pflueger, M.D., San Francisco.....	731
Osteogenesis: An Experimental Study. J. Dewey Bisgard, M.D., Omaha..	748
Fabella (Sesamoid in the Lateral Head of the Gastrocnemius). Charles J. Sutro, M.D.; Maurice M. Pomeranz, M.D., and Sydney M. Simon, M.D., New York .....	777
Epilepsy Secondary to Head Injury. Mark Albert Glaser, M.D., and Frederick P. Shafer, M.D., Los Angeles.....	783
Injuries to the Crucial Ligaments. Henry Milch, M.D., New York.....	805
Lymphogranuloma Inguinale: Its Relation to Stricture of the Rectum. Warren Rainey, M.D., and Warren H. Cole, M.D., St. Louis.....	820
Combined and Separate Effects of Bile, Pancreatic Secretion and Trauma in Experimental Peptic Ulcer. Amos M. Graves, M.D., San Antonio, Texas	833
Chronic Ulcerative Colitis with Associated Carcinoma: Progress in Management. J. Arnold Barger, M.D., and Claude F. Dixon, M.D., Rochester, Minn. ....	854
Hepatic Function: III. Effect of Cholecystectomy on Hepatic Function. A. Cantarow, M.D.; E. Gartman, M.D., and G. Ricchiuti, M.D., Philadelphia	865
Effect of Jejunal Feeding on Gastric Acidity. A. A. Appell, M.D., Toronto, Canada .....	875
Effect of Enemas on Intestinal Motility. Hjalmer E. Carlson, M.D., and Thomas G. Orr, M.D., Kansas City, Mo.....	881
A Review of Urologic Surgery (to be Concluded). Albert J. Scholl, M.D., Los Angeles; E. Starr Judd, M.D., Rochester, Minn.; Jean Verbrugge, M.D., Antwerp, Belgium; Alexander B. Hepler, M.D., Seattle; Robert Gutierrez, M.D., New York, and Vincent J. O'Connor, M.D., Chicago.....	884
Correspondence:	
Continuous Intravenous Injection. J. Shelton Horsley, M.D., Richmond, Va. ....	908

## JUNE 1935. NUMBER 6

Tumor of the Neuromyo-Arterial Glomus: Report of Cases. Victor Raiman, M.D., and Leo Mayer, M.D., New York.....	911
Otogenous Abscess of the Parietal Lobe: Review of the Literature and Report of Six Cases. Cyril B. Courville, M.D., and J. M. Nielsen, M.D., Los Angeles .....	930

# CONTENTS OF VOLUME 30

## JUNE—Continued

	PAGE
Diagnosis of Neurogenic Lesions of the Urinary Bladder by Cystometry: An Appraisal of the Method Based on Experimentation with Animals. J. M. McCaughan, M.D., and J. H. Hershey, M.D., St. Louis.....	956
Vaso-Orchidostomy with Interposed Spermatocoele: A Procedure for Treatment of Sterility. Seymour F. Wilhelm, M.D., New York.....	967
Melanosis Coli: Its Clinical Significance. Alfred J. Zobel, M.D., and David A. Susnow, M.D., San Francisco.....	974
Gangrene of the Buttock, Perineum and Scrotum Due to Endamoeba Histolytica: Report of a Case. Frank L. Meleney, M.D., New York, and Henry E. Meleney, M.D., Nashville, Tenn.....	980
Lumbar Vertebral Epiphysitis. Samuel Kleinberg, M.D., New York.....	991
Surgical Treatment of Ependymal Glioma of the Spinal Cord. Leo J. Adelstein, M.D., and George H. Patterson, M.D., Los Angeles.....	997
Use of Low Temperatures in Culture and Transportation of Surgical Maggots. S. W. Simmons, B.Sc., M.A., Washington, D. C.....	1015
Adequacy of Nutritional Retardation in Culture of Sterile Maggots for Surgical Use. S. W. Simmons, B.Sc., M.A., Washington, D. C.....	1024
Peritoneal Drainage: Resistance of Sinus Tract to Infection. Philip Shambaugh, M.D., and Robert Boggs, M.D., Boston.....	1032
Penetration of Moist Heat Applied to the Abdomen and Its Effect on Intestinal Movements. Hjalmar E. Carlson, M.D., and Thomas G. Orr, M.D., Kansas City, Kans.....	1036
Suction with a Nasal Catheter: Its Effect on the Blood Chemistry: Report of a Case. Richard F. Northrop, M.D., Philadelphia.....	1040
Acute Pancreatitis. Francis F. Henderson, M.D., and E. S. A. King, M.D., Boston .....	1049
A Review of Urologic Surgery (Concluded). Albert J. Scholl, M.D., Los Angeles; E. Starr Judd, M.D., Rochester, Minn.; Jean Verbrugge, M.D., Antwerp, Belgium; Alexander B. Hepler, M.D., Seattle; Robert Gutierrez, M.D., New York, and Vincent J. O'Connor, M.D., Chicago.....	1058
General Index .....	1085

# ARCHIVES OF SURGERY

VOLUME 30

JANUARY 1935

NUMBER 1

## THERAPEUTIC USE OF THE CONCENTRATED STREPTOCOCCUS SERUM OF THE NEW YORK STATE DEPARTMENT OF HEALTH

IN PATIENTS WITH INFECTIONS OF THE EAR, NOSE AND THROAT

ADELE E. SHEPLAR, M.D.

MARTHA JANE SPENCE, M.A.

AND

WARD J. MacNEAL, M.D.

NEW YORK

Inflammatory disease of the upper respiratory region is exceedingly common and in a considerable portion of the patients hemolytic streptococci are present on the mucous membrane in abundance and are evidently etiologically related to the disorder. When the infection extends to the middle ear, the mastoid, the bronchi and the adjacent parenchyma of the lung or to the blood stream, one is not infrequently able to detect streptococci in pure culture in these new situations, a circumstance which offers strong evidence implicating the streptococcus as an important inflammatory agent at the original site, where it had been associated with other microbes. The use of streptococcus serum in the treatment of infections of the upper respiratory tract seems to have been somewhat neglected, except when these inflammations have been associated with the clinical manifestations leading to a diagnosis of erysipelas or of scarlet fever. We are inclined to a somewhat different point of view and favor employing streptococcus serum whenever there is good reason to believe that virulent streptococci are concerned in the causation of dangerous inflammation, regardless of the particular classic clinical entity under guise of which it appears. This point of view may be more clearly elucidated after a consideration of the individual patients.

Among our twenty-six patients treated with the concentrated serum of the laboratory of the New York State Department of Health there are eight which have been allocated to this category of infections of the ear, nose or throat, although one of them apparently had his initial

---

This work was made possible by a grant from the Josiah Macy Jr. Foundation. From the Department of Pathology and Bacteriology, New York Post-Graduate Medical School and Hospital, Columbia University.

The patients whose records are utilized in this paper were treated in the clinical services of the following physicians: Dr. A. G. De Sanctis, Dr. S. C. Glasgow, Dr. J. E. Hutton and Dr. D. Macpherson.

lesion low in the esophagus. The serum treatment was initiated at an advanced stage of the disease as a rule. Of the eight patients, two died and six survived.

#### REPORT OF CASES

CASE 1.—S. W., a girl, aged 4 months, became ill on March 7, 1933, with a swollen lymph node in the neck and high fever. On admission to the hospital on March 11, severe purulent rhinitis and bilateral purulent otitis media were recognized. The abridged clinical record is shown in chart 1. Spinal tap immediately after admission yielded a normal spinal fluid. The right ear drum was incised on March 13. On March 16 a blood culture was taken, and 20 cc. of human blood was given by intramuscular injection. The blood culture became positive on March 17, showing eighty-five colonies of hemolytic streptococci per cubic centimeter of blood. On this day the left middle ear was opened, and one-half ampule (10,000 units) of the concentrated streptococcus serum was given by intramuscular injection. On March 18 left mastoidectomy was done, with ligation of the left jugular vein and removal of a thrombus from the left lateral sinus. A transfusion was given before the operation and another on March 20. On March 21 there was recognized pneumonia on the right side, and the left arm became blue and

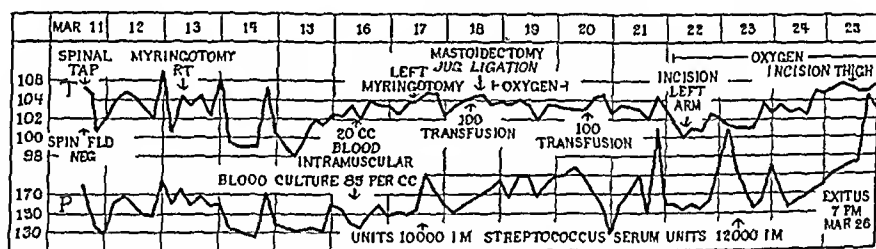


Chart 1.—Abridged clinical record of S. W., a girl, aged 4 months. This patient had a positive blood culture taken on March 16. On the following day 10,000 units of serum was given by intramuscular injection. No further serum was given until March 23, when another dose of 12,000 units was given intramuscularly. In the interval there was an operation on the mastoid with ligation of the jugular vein on March 18. The child died on March 26.

tensely swollen. Aspiration of the arm was performed and an incision made on March 22, a large amount of purulent exudate containing streptococci being evacuated. Another intramuscular injection of the streptococcus serum, 12,000 units, was administered on March 23. On the next day the site of the injection on the left buttock appeared necrotic. An abscess of the right thigh was opened on March 25. Oxygen was given on March 18 and 19 and again from March 22 until death on March 26.

Necropsy revealed, in addition to the disease of the left mastoid region, active purulent mastoiditis on the right side and extending from it a dissecting abscess (von Bezold) along the carotid sheath into the mediastinum to the soft tissues about the shoulder and down the left arm, septic infarcts of both lungs with fibrinopurulent pleurisy on the right side, metastatic abscesses in both thighs and the left buttock and septic changes in the various organs. The cardiac valves were normal.

CASE 2.—A. G., a boy, aged 11 months, had his right ear drum incised on March 19, 1933, and again on March 22. A purulent discharge continued until about March 25, and during this time the temperature ranged from 101 to 103 F.

On March 31 the mother noticed that the right lower extremity remained flexed, and attempts to straighten it evidently caused pain. From March 30 to April 9 the temperature observed at home ranged from 100 to 101 F. The baby was admitted to the hospital at 11 a. m. on April 9, on account of the deformity of the leg. The abridged clinical record is shown in chart 2.

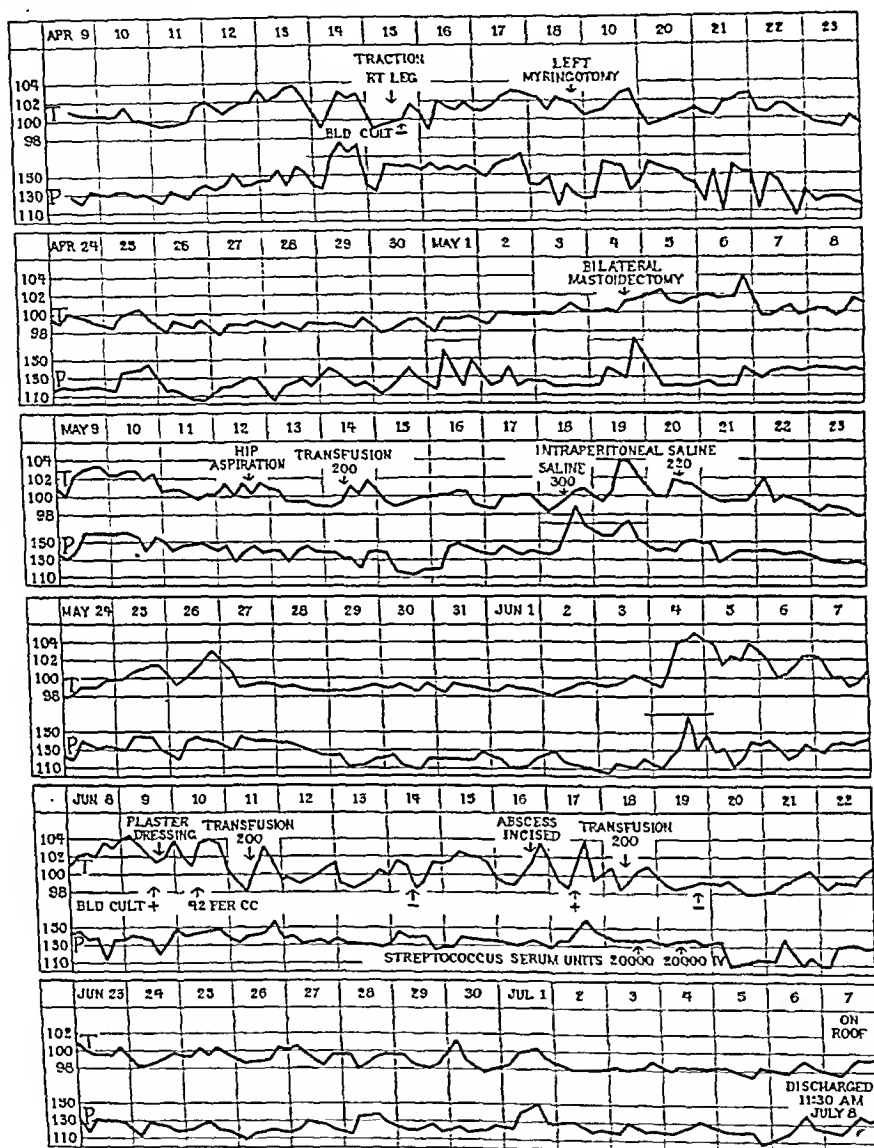


Chart 2.—Abridged clinical record of A. G., a boy, aged 11 months. The illness began with otitis media about the middle of March. Subsequently there was some disability of the right leg, for which the patient was admitted to the hospital. Bilateral mastoidectomy was performed on May 4. A positive blood culture was obtained for the first time on June 9. The serum was administered on June 18 and June 19, a total of 40,000 units intravenously. The child was discharged on July 8 in good condition. There was no serum reaction.



Examination on admission disclosed little in addition to the foregoing data. The flexion at the right hip and knee was not associated with recognizable swelling, redness or induration. Roentgenologic study, however, revealed evidence of marked synovial distention of the right hip joint on April 9 and on April 18 destructive arthritis and epiphysitis, apparently of metastatic origin. The right ear was no longer draining, but on April 18 the left ear drum was incised to facilitate drainage, which had already been initiated spontaneously. On May 4 bilateral mastoidectomy was performed. There was mucopurulent exudate in each mastoid, and hemolytic streptococci were recovered from these exudates. The aspiration of the hip on May 12 failed to disclose any fluid.

Without any apparent reason there was a sharp rise in temperature on June 4. On June 9 the right lower extremity was enclosed in a plaster dressing, and on this day a blood culture was taken. This proved to be positive for hemolytic streptococci. Another blood culture taken on June 10 yielded 42 colonies per cubic centimeter of blood. A blood culture taken on June 14 remained sterile. On June 16 a large abscess on the back, just above the plaster dressing, was opened. This contained streptococci. A blood culture taken on the following day was positive. Transfusions were given on May 14, June 11 and June 18. The concentrated streptococcus serum was given intravenously, 20,000 units on June 18 and a similar dose on June 19. Convalescence was gradual from this time, and the patient was discharged on July 8, being allowed to bear weight on the plaster dressing at this time. There was no urticaria or other evidence of serum sickness following the injection of the serum.

CASE 3.—M. S., a girl, aged 4 years, became ill on May 5, 1933, with rhinitis. Three days later a small abscess on the right side of the nose was lanced. She was admitted to the hospital on May 9, at which time the nostrils were occluded by edema and congestion, and many enlarged lymph nodes were recognized in the neck, especially along the left carotid chain. The abridged clinical record is shown in chart 3.

A blood culture taken on May 9 gave a positive growth of hemolytic streptococci. A transfusion was given on May 11. Roentgenologic study revealed capsular distention of the right hip joint without evidence of changes in the bones. On May 12 the concentrated streptococcus serum of the laboratory of the New York State Department of Health was injected, first into the skin, revealing a positive sensitiveness to horse serum, then subcutaneously and then intramuscularly. One ampule of 20,000 units was administered daily from May 12 to 16, inclusive. A blood culture taken on May 16 was again positive, the colonies on the plates being recorded as "innumerable." An eruption of small pustules appeared on May 19, and the patient became irrational. On May 22 an abscess on the heel was incised, and pus containing streptococci was evacuated. Following this there were cyanosis and delirium. An abscess of the left arm was opened on May 27. A blood culture taken on May 29 revealed 3 streptococci per cubic centimeter of blood, and another blood culture taken on May 31 remained sterile. Transfusions were given on May 11, 17, 24 and June 7. The patient was discharged on June 12.

Progress at home was not satisfactory, and the child was returned to the hospital on June 16 because of pain in the left hip. Roentgenologic study revealed osteomyelitis of the left femur. This was treated surgically without use of further serum, and the patient was finally discharged, improved, on August 10.

Among the unusual features of this record, one may mention the early recognition of the bacteremia, the sensitiveness of the patient to

horse serum, the effective desensitization, the absence of subsequent serum sickness and the eventual survival of the patient. We are inclined to think that intravenous injection of the later doses of serum might have been better than use of the intramuscular route. The wisdom of further injections of the serum may be open to debate. We are inclined to favor larger doses continued over a longer period for an actual streptococcal bacteremia. Possibly the unfortunate sequel of osteomyelitis might thus have been avoided. One should note that the right hip joint appeared to be threatened early but that the late bone lesion appeared in the left femur.

CASE 4.—M. C., a boy, born on Dec. 13, 1928, had been subject to vomiting since the age of 2 weeks. On March 12, 1931, he swallowed a cherry stone, and subsequent to that no solid food was retained and even liquids were regurgitated

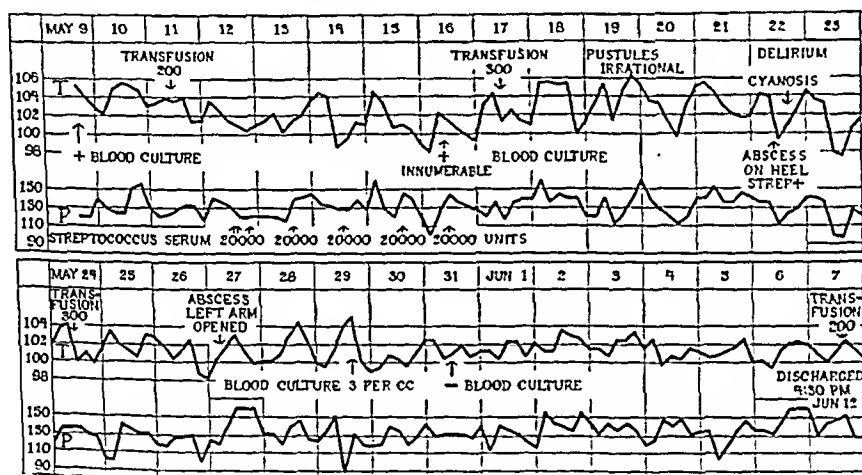


Chart 3.—Abridged clinical record of M. S., a girl, aged 4 years. The illness started with an infection of the upper respiratory tract. A blood culture taken on the day of admission was positive. Serum was administered on May 12, 13, 14, 15 and 16, a total of 100,000 units. The patient had a stormy convalescence, but was discharged on June 12. She returned to the hospital on June 16 with osteomyelitis of the left femur and was finally discharged improved on August 10. It appears that the amount of serum given was somewhat too small in this case.

frequently. On March 24 he came to the hospital and at that time there was discovered an esophageal stricture  $8\frac{1}{2}$  inches (21.5 cm.) from the upper incisor teeth with an enormous dilatation above it and a foreign body, recognized as a cherry stone, caught in the stricture. After this he returned to the hospital at frequent intervals for dilation of the stricture. On March 9, 1933, he came for his usual treatment, consisting of esophagoscopy and dilation with bougies. On March 23 he came for another treatment, but at this time the esophagoscopic examination revealed ulceration at the cardiac end of the stricture. Bougies were therefore not passed, but a Senn gastrostomy was performed on March 28 in order to favor healing of the ulcer. This healing progressed favorably, so that the stricture of the esophagus was dilated from below through the gastrostomy

on April 13 and again on April 20. The child was sent home, but returned again on April 27 for a third dilation from below. He came again on May 4 for a dilation, but because he had been taking food by mouth the treatment was canceled and he was sent home at 1 p. m. on May 5, his morning temperature having been 99.4 F. On the same day he was readmitted to the hospital at 4:10 p. m., severely ill, with a temperature of 104.2 F., which rose to 105.4 F. at 8 p. m.

The abridged clinical record is shown in chart 4. Spinal tap at 9 p. m. on May 5 yielded a negative fluid, and a blood culture taken on May 9 remained sterile. However, the blood culture taken on May 11 gave a growth of hemolytic streptococci, and blood cultures on May 13 and 16 were also positive, the latter showing 52 colonies per cubic centimeter of blood. The concentrated streptococcus serum was given intravenously, one ampule daily from May 12 to 16, inclusive, the total amounting to 100,000 units. The patient was given a transfusion on May 12 and 17. There was no perceptible response to these therapeutic measures, and death took place early on the morning of May 22.

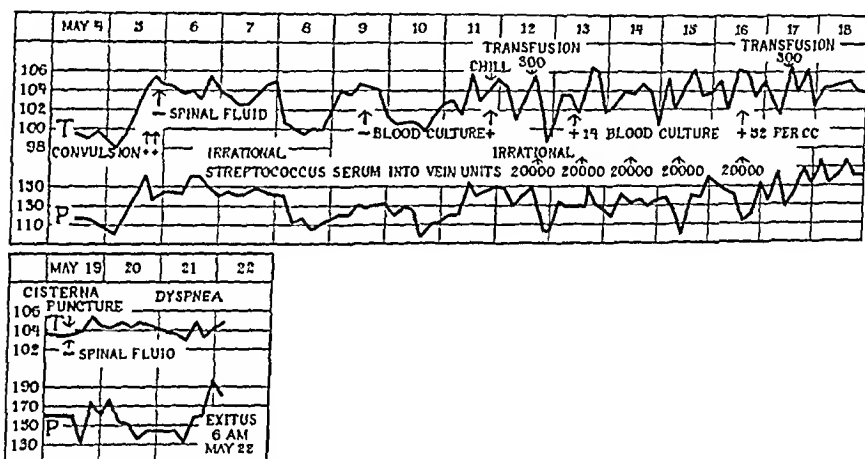


Chart 4.—Abridged clinical record of M. C., a boy, aged 5 years. This child was under treatment for stricture of the esophagus. On May 5 there evidently developed a severe infection extending from the esophageal stricture. A blood culture taken on May 11 was positive. Serum was given on May 12, 13, 14, 15 and 16, a total of 100,000 units. The child died on May 22. Necropsy revealed bilateral empyema and vegetative endocarditis, apparently taking origin from the ulcerated esophageal stricture.

Necropsy disclosed: complete ulceration of the esophagus throughout the constricted portion which extended from the level of the uppermost part of the aortic arch to the cardia, with marked fibrous thickening of the wall of the esophagus; mediastinal lymphadenitis; bilateral empyema; acute vegetative lesions on the mitral, aortic and tricuspid valves, and multiple septic infarcts of both lungs, along with other signs of general sepsis.

CASE 5.—F. C., a girl, aged 6 years, received a bruise in the lower abdominal region on hitting the corner of a table on Jan. 14, 1933, and this was followed by appearance of blood at the vulval outlet. Two days later an appendectomy was performed, and the postoperative course was uneventful until the ninth day, when the temperature rose to 104 F. and the pharynx was found to be inflamed. After four days the fever subsided, but the sore throat and tenderness of the

muscles of the neck persisted. The child was taken home on January 31. She had chills with a rise of temperature to 102 F. every two or three days. Between times she appeared well except for vague pains in the joints and stiffness of the neck. On February 12, at noon, she had a chill with a rise in temperature to 104 F. By evening the temperature was normal. The evening specimen of urine was filled with blood. The patient was admitted to the Post-Graduate Hospital for the first time on February 14, at which time there were recognized slight coryza, a reddened pharynx and enlarged cervical lymph nodes.

The abridged hospital record is shown in chart 5. On February 15, at 1 p. m., there was a chill followed by a rise in temperature to 104 F. A blood culture taken on February 16 produced a growth of hemolytic streptococci in twenty-four hours. When this was recognized on February 17, another blood culture was taken, bacteriologic examination of the urine was undertaken and one ampule of concentrated streptococcus serum was given by intramuscular injection. On the next day a transfusion was given, and the dose of serum was repeated. A blood culture taken on February 20 remained sterile. There were no further chills. After February 28 the highest temperature observed was 99.6 F. The patient was discharged on March 7, without a definite understanding having been reached of the disorder from which she seemed to have recovered. The traumatic factor in the history seems problematic; the possible influence of the appendectomy is

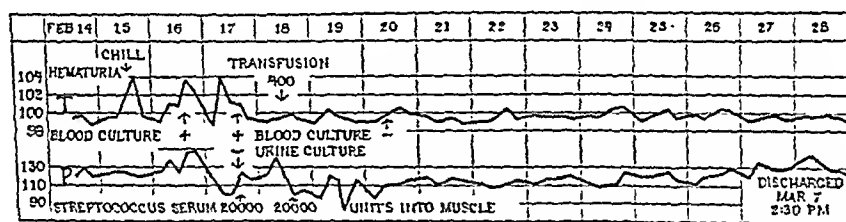


Chart 5.—Abridged clinical record of F. C., a girl, aged 6 years. This child was admitted on account of hematuria. A positive blood culture was obtained on February 16 and again on February 17. The serum was administered on February 17 and February 18, a total of 40,000 units. The recovery was very prompt.

uncertain. Perhaps inflammation of the upper respiratory tract with extension of streptococcal infection to the lymphatics and to the blood stream, complicated by hemorrhagic nephritis, may fit the situation. At any event, the improvement of the patient following the injection of the serum and the transfusion was dramatic.

CASE 6.—E. T., a girl, aged 20, was admitted to the hospital on April 6, 1932 (chart 6), and a right mastoidectomy with exposure of the lateral sinus was performed. On April 10 the patient complained of frontal headache, and on April 11 the temperature continued to mount, reaching 105 F. at 4 p. m. A blood culture taken at 1:30 p. m. on this day showed a positive growth of hemolytic streptococci. Spinal tap at 7 p. m. on April 11 yielded a normal spinal fluid. A transfusion was given at 9 p. m. On April 12, at 5 a. m., there was a chill lasting twenty minutes with a rise in temperature to 106.4 F. On this day the right lateral sinus was again exposed, and free bleeding was obtained from its upper portion. Incision was then made in the neck; the right jugular vein and its facial branch were ligated and severed. On April 15 an area of erysipelas was recognized about the right ear. The patient complained of abdominal pain and difficulty in swallowing. On April 16 the area of redness had extended to include the

cyclids and the lower portion of the forehead. It was edematous with a sharply defined margin. Erysipelas antitoxin (commercial), 500,000 skin units, was given subcutaneously on this day. The patient was very weak and unable to swallow fluids. On this account a duodenal tube was inserted for about twenty-four hours. A blood culture taken on April 18 again gave positive growth of hemolytic streptococci. On April 26 the blood culture was positive, yielding 16 colonies per cubic centimeter of blood. On April 28 the patient was cyanotic, with a feeble pulse, and was apparently in a desperate condition. Transfusion was given on April 29. The concentrated streptococcus serum of the New York State Department of Health was given for the first time on April 30, first a minute intracutaneous dose at 1:30 p. m., which revealed a marked hypersensitiveness. This was followed by an intravenous dose of 1 cc. at 2 p. m., and at 5 p. m. an intravenous dose of 3 cc. The patient had a chill lasting thirty minutes. The serum treatment was continued, 5 cc. on May 1, two doses of 5 cc. each on May 2 and a final dose of 5 cc. on May 3, all intravenously. The total amount was 60,000 units,

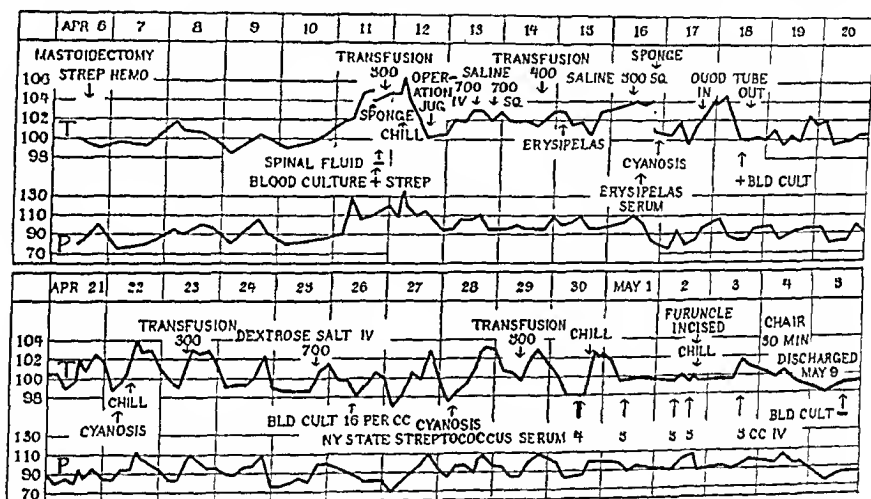


Chart 6.—Abridged clinical record of E. T., a woman, aged 20. This patient gave a positive blood culture on April 11 following a mastoidectomy on April 6. The jugular vein was ligated on April 12. Transfusions were given on April 11 and April 14. A commercial erysipelas serum was administered on April 16 on account of a cutaneous eruption which had been recognized the day before. The blood culture remained positive on April 18 and April 26. On April 30 intravenous serum therapy was begun, a total amount of 24 cc., equivalent to 60,000 units, being administered in four days by intravenous injection. The patient was discharged in good condition on May 9.

the titer of the concentrated serum being 2,500 units per cubic centimeter. A furuncle on the left buttock, incised on May 2, yielded pus containing only *Staphylococcus albus* but no streptococci. A blood culture taken on May 5 remained sterile. The patient was discharged May 9, in good condition.

CASE 7.—D. M., a nurse, aged 21, became ill with a sore throat on Feb. 5, 1933, and with pain in both ears on February 7. She was admitted to the hospital on February 8, on which day her temperature reached 103 F. Her abridged clinical record is shown in chart 7. After an uneventful week, on February 14 a

red and tender area appeared just below the right knee. On the next day, similar but somewhat smaller red tender areas appeared on both legs and on the hands. The eruption was diagnosed by a dermatologic consultant as erythema nodosum of infectious origin. The patient gave a history of a similar eruption four years before, with a streptococcic sore throat. On February 15, while undergoing an irrigation of the right antrum, she fainted, and two days later after treatment of her nose she went into an alarming collapse, with pale face and lips, profuse diaphoresis, a rapid and feeble pulse and apparent unconsciousness. The pupils were not dilated, and they reacted to light. She rallied quickly. On February 20 the eruption had extended above the elbows and knees. The joints were tender, and there was a purulent discharge from the nose in which abundant hemolytic streptococci were recognized on culture. A blood culture taken on February 21 was negative. On February 22 the concentrated streptococcus serum was given in divided doses to insure desensitization, the total amount on this day being 40,000 units subcutaneously. A similar amount was given the next day in two doses. The temperature reached 103.8 F. and the pulse 120 per minute at 8 p. m., two

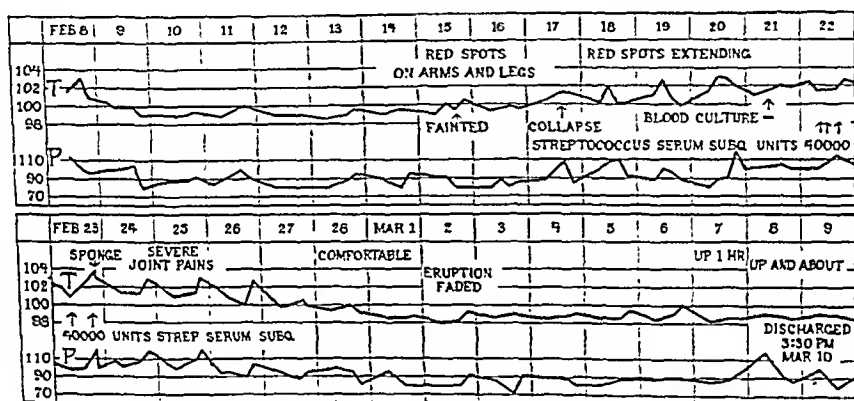


Chart 7.—Abridged clinical record of D. M., a woman, aged 21. This patient had a severe rhinitis involving the sinuses. On February 15 an eruption developed which was diagnosed as erythema nodosum. The blood culture remained negative. The patient received streptococcus serum, 40,000 units on February 22 and 40,000 units on February 23, all subcutaneously. Her recovery was satisfactory.

hours after the last injection of serum. On February 24 the joints of the hands and feet became painful. The cutaneous lesions ceased to extend but remained painful to the touch. The patient was very uncomfortable. By February 27 these manifestations had subsided, and the use of codeine was discontinued. Irrigation of the right antrum brought out a large amount of green pus. By March 5 the nasal inflammation had subsided. The patient was up and about on March 8 and was discharged on March 10. There was no late serum reaction.

CASE 8.—J. L., a man, aged 48, first presented himself in the outpatient service on Feb. 8, 1933, on account of persistent cough, pain on swallowing and the coughing of blood. Examination revealed edema over the arytenoids, especially the right, with thickening of the mucous membrane in the interarytenoid space and in the right pyriform sinus. A biopsy specimen taken on February 13 revealed a noncornifying squamous cell carcinoma. On February 23, a more thorough laryngoscopic examination under local anesthesia disclosed ulceration and general

infiltration of the laryngeal surface of the epiglottis reaching as far as the lingual surface, and extension of the new growth downward and forward to the right side of the larynx and right pyriform sinus. Examination again under anesthesia on March 13 showed carcinoma involving the larynx and the oropharynx. The laryngeal portion of the pharynx appeared not to be invaded. On April 3 the patient was admitted to the hospital for radical operation. His abridged hospital record is shown in chart 8.

On April 5 a total laryngectomy and pharyngotomy were performed. A tube was passed through the nose into the duodenum and left in place for feeding. A tracheotomy tube was inserted into the trachea. The communication between the esophagus and the trachea was filled with molded paraffin attached to the tracheotomy tube. A rubber drain was left on each side of the neck. The operation required four hours and twenty-five minutes and was finished at 5:55 p. m. Two days later the coughing increased so as to be almost continuous; there was abundant thick mucus present, and the patient appeared to become gradually exhausted. Bacteriologic study of the exudate and of the tracheal mucus taken on April 8

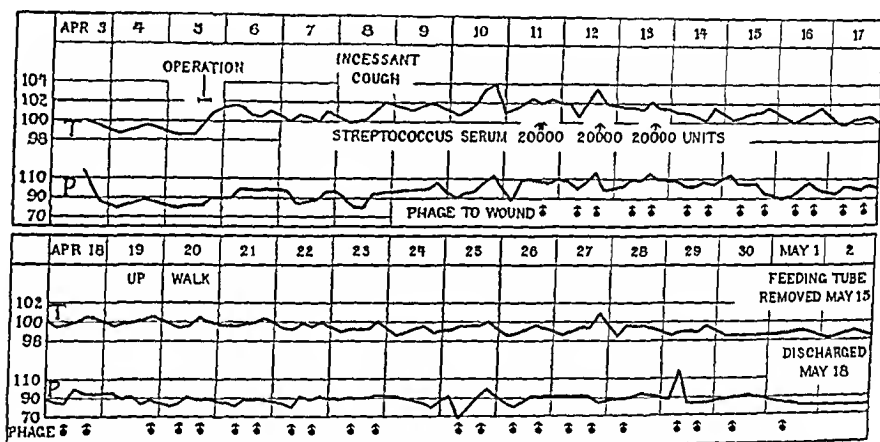


Chart 8.—Abridged clinical record of J. L., a man, aged 48, operated on for carcinoma of the larynx extending into the pharynx, on April 5. Following the operation he did badly, and the outlook appeared serious on April 11. Streptococcus serum was given on April 11, 12 and 13, and staphylococcus bacteriophage was applied to the wounds repeatedly. The patient made an excellent recovery and at the last report had remained without recurrence.

revealed chiefly hemolytic streptococci with somewhat less abundant staphylococci. On April 11, the concentrated streptococcus serum was given in divided doses, intracutaneously and subcutaneously, the total amount being 20,000 units, and on the same day application of staphylococcus bacteriophage to the surfaces of the wound was begun. The injection of the serum was repeated on April 12 and April 13, and the application of the bacteriophage was continued to May 1. The hopeless aspect of the situation changed quickly. The patient was up and about after April 19. The feeding tube was dispensed with on May 15, and the patient was discharged on May 18. He has returned periodically to the outpatient service and, according to recent reports, is leading an active life without evident recurrence of the neoplasm.

## COMMENT

The eight patients selected for presentation in this paper do not represent a homogeneous group but they have one feature in common, namely, a clinical interest for the specialist in otorhinolaryngology. The presenting signs and symptoms caused the patients to be assigned to the otorhinolaryngologic services. Of the eight patients, six were allowed to reach a stage of invasion of the blood stream by hemolytic streptococci before the serum was administered. In the other two patients there was no positive blood culture. There were two deaths and six survivals.

As a rule, the serum therapy was begun by small doses, the first one being administered intracutaneously as a test for hypersensitiveness to horse serum, followed after a half an hour by a small subcutaneous dose. After this we gave the full dosage to those persons who were not hypersensitive, but proceeded with more caution in those showing an urticarial wheal at the intracutaneous site. Intravenous, intramuscular and subcutaneous routes were employed. We favor the former for prompt effect and prefer the subcutaneous route in hypersensitive patients and in cases in which the situation does not demand prompt effect.

Untoward effects which may be ascribed to the horse serum itself were observed in three patients. M. S., aged 4 years, reacted with an urticarial wheal to the initial intracutaneous injection of serum. The continuation of the serum treatment by subcutaneous and intramuscular routes was free from any other untoward manifestations. E. T., aged 20, had received an injection of erysipelas serum on April 15 and on that account was expected to be hypersensitive to horse serum on April 30, when the concentrated serum was used. Actually, the initial intracutaneous injection at this time did disclose a marked hypersensitiveness. However, because of the desperate state of the patient, the second injection of 1 cc. was given intravenously after an interval of thirty minutes and a third intravenous injection of 3 cc. three hours later. Following this there was a chill lasting thirty minutes and a rise in temperature to 102.6 F. However, the subsequent intravenous injections of 5 cc. each were without evident reaction, and there was no late cutaneous rash. D. M., aged 21, appeared not to be hypersensitive on intracutaneous injection of the serum on February 22. However, she suffered pains in her joints on February 24 and 25, which may have been caused by the serum. There was no late cutaneous rash. In this series, therefore, the serum reactions did not cause any grave disturbances.

The two fatalities deserve special consideration. Both patients were young children. S. W., aged 4 months, was the victim of an infection of the upper respiratory tract, otitis media and mastoiditis. After a



positive blood culture taken on the tenth day of the illness a single intramuscular injection of 10,000 units of the concentrated serum was given on the following day. A day later the left mastoid was opened and the left jugular vein ligated. Another dose of 12,000 units of serum was given on March 23, the sixth postoperative day. Autopsy disclosed advanced destruction of the right mastoid with a dissecting abscess extending from it to the mediastinum. The second fatality occurred in a boy, M. C., aged  $4\frac{1}{2}$  years, who had been subjected to repeated instrumental esophageal dilations for congenital stricture. In this case we were confronted with an acute vegetative endocarditis due to the hemolytic streptococcus, apparently a sequel of a chronic inflammation in the mediastinum about the malformed and ulcerated esophagus. In both of these patients the serum treatment was a failure. What might have been accomplished by earlier adequate doses of the serum is a matter for conjecture.

Two of the patients survived with persistent disease of the bone. In one of them, A. G., 11 months of age, destructive arthritis and epiphysitis developed at the right hip early in April, almost two months before the positive blood culture was first obtained. The serum was administered subsequent to the positive blood culture. The other one, M. S., aged 4 years, received 100,000 units of the serum from May 12 to 16 after a positive blood culture taken on May 9. Almost two weeks after the last injection of serum the blood culture still revealed 3 colonies per cubic centimeter of blood, and a month after the last dose osteomyelitis of the left femur became manifest. The experience with these two patients led us not only to favor early administration of the serum in adequate dosage but also to continue the injections in smaller amounts over several weeks in the streptococcic infections of the blood stream in children in order, if possible, to afford protection to the skeleton as well as to other important structures.

The remaining two patients with septicemia recovered without serious sequelae. F. C., aged 6 years, recovered so promptly following 40,000 units of the concentrated serum and one transfusion that one would be skeptical about the diagnosis of bacteremia were it not for the two positive blood cultures. The other patient, E. T., aged 20, had a prolonged sepsis which appeared to have been ameliorated by the commercial streptococcus serum given for the erysipelas on April 16. However, the bacteremia persisted until, as a measure of desperation, the concentrated serum was given intravenously, with a dramatically favorable result. This patient was ill in 1932, when our experience with this serum was still limited.

Of the eight patients, the two oldest, D. M. and J. L., escaped without recognized bacteremia. D. M., a nurse, aged 21, was ill enough

for consultation in which the bacteriologists were included, and the suggestion to employ serum was accepted. The subsequent course of the illness was highly gratifying, but the part played by the serum may be questioned. We think that it helped considerably. J. L., aged 48, subjected to an extensive mutilating operation for radical removal of a laryngeal carcinoma already extrinsic, suffered the usually unavoidable infection of the operative site with the pharyngeal bacteria. An apparently desperate condition was promptly relieved during the use of the concentrated streptococcus serum in combination with local application of staphylococcus bacteriophage to the wound, and we are inclined to the belief that these agents contributed an essential part to this relief, an opinion also shared by the surgeons in the case.

The records of the eight patients here discussed offer strong evidence in favor of the use of streptococcus serum, particularly the concentrated streptococcus serum of the New York State Department of Health, in the treatment of streptococcic infections of the respiratory tract, ear and mastoid, as well as the infections of the blood stream developing as sequelae to these. We hope to persuade our clinical friends in this field to employ the serum earlier and in adequate dosage so as to forestall these more dangerous sequelae rather than to await a desperate or well-nigh hopeless situation before considering serum therapy. Early bacteriologic examination leading to a prompt recognition of the infecting organisms is the obvious key to this type of therapy.

#### SUMMARY

1. Eight patients suffering from severe infection with hemolytic streptococci in the field of otorhinolaryngology, six of them with positive blood cultures, were treated with the concentrated streptococcus serum of the New York State Department of Health, with two deaths and six recoveries.

2. The early use of this serum is indicated in streptococcic infections of the upper respiratory tract and the middle ears in order to forestall the all too common serious sequelae of these maladies.

3. Postoperative infections in the upper respiratory tract may also be favorably influenced by this serum.

# RELATIONSHIP OF INFECTION TO POSTOPERATIVE PULMONARY COMPLICATIONS

W. D. SUTLIFF, M.D.

Assistant Physician, Thorndike Memorial Laboratory, Boston City Hospital;  
Instructor, Department of Medicine, Harvard Medical School

CHICAGO

AND

BRANDT F. STEELE, M.D.

Research Fellow, Thorndike Memorial Laboratory, Boston City Hospital;  
Assistant Resident, Fifth Surgical Service (Harvard)

BOSTON

Recent studies of postoperative pulmonary complications have indicated that bronchopneumonia, bronchitis and collapse of portions of the lung show the highest incidence.<sup>1</sup> These three complications may logically be considered together since they occur together postoperatively and have long been observed by pathologists in the same lungs.<sup>2</sup> It seems possible that they have certain etiologic factors in common.

A thorough study of such etiologic factors as infection, diminished ventilation of the lungs and bronchial obstruction has shown that no single one adequately explains the development of pulmonary complications. Infection by pneumococci occurs regularly in postoperative bronchopneumonia,<sup>3</sup> but the invasiveness of the organisms is of such low degree that their entrance into the lungs and their proliferation are probably aided by other conditions. Although diminution in the venti-

---

Funds for this investigation were supplied by the Influenza Commission of the Metropolitan Life Insurance Company.

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), and the Fifth Surgical Service (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

1. King, Donald S.: Postoperative Pulmonary Complications: I. A Statistical Study Based on Two Years' Personal Observation, *Surg., Gynec. & Obst.* **56**:43, 1933. Fuller, C. J.: Analysis of Pulmonary Complications Based upon Cases at the University College Hospital, London, in One Year, *Lancet* **1**:115 (Jan. 18) 1930.

2. Gairdner, W. T.: On the Pathologic States of the Lung Connected with Bronchitis and Bronchial Obstruction, *Month. J. M. Sc.* **11**:122 and 230, 1850; **12**:440, 1851; **13**:2 and 238, 1851.

3. (a) Whipple, A. O.: A Study of Post-Operative Pneumonitis, *Surg., Gynec. & Obst.* **26**:29, 1918. (b) Cleveland, M.: Further Studies in Post-Operative Pneumonitis, *ibid.* **28**:282, 1919. (c) Gundel, M.: Bakteriologische Untersuchungen an Leichenlungen unter besonder Berücksichtigung ihrer Bedeutung für das Pneumonie Problem, *Ztschr. f. Hyg. u. Infektionskr.* **112**:623, 1931.

lation of the whole lung is an important predisposing cause, it is not more marked in cases in which complications develop than in those in which no complications occur.<sup>4</sup> Collapse of the lungs is primarily the result of bronchial obstruction.<sup>5</sup> Yet obstruction by a mucous plug of any passage smaller than a primary bronchus is ineffective unless there is simultaneous interference with collateral respiration between alveoli.<sup>6</sup> It is also true that both the production and the subsequent injurious effects of mucous plugs are largely conditioned by the presence of infectious agents. Conclusive evidence that collapse is the usual precursor of bronchopneumonia has not been obtained. It seems more than likely that the complications to be considered are not due to a single cause but to the interaction of two or more causative factors. In this study particular attention has been devoted to the interrelationships of infection and diminished ventilation.

A series of patients among whom a high incidence of the more common postoperative pulmonary complications might be expected to occur were observed. Pulmonary changes of slight degree, as well as clearly defined complications, were noted by physical and roentgenologic examinations. In the same patients a systematic study of the well known pathogenic bacteria of the nasopharynx was undertaken.

#### PULMONARY CHANGES FOLLOWING OPERATION

*Procedure.*—Sixteen patients about to undergo operations on the upper part of the abdomen were selected for observation, as about 10 per cent of such patients have definite postoperative pulmonary complications.<sup>1</sup> The preliminary period of observation in the hospital which

4. (a) Muller, G. P.; Overholt, R. H., and Pendergrass, E. P.: Post-Operative Pulmonary Hypoventilation, *Arch. Surg.* **19**:1322 (Dec., pt. 2) 1929. (b) Powers, John H.: Vital Capacity: Its Significance in Relation to Post-Operative Pulmonary Complications, *ibid.* **17**:304 (Aug.) 1928. (c) Churchill, E. D., and McNeill, D.: The Reduction in Vital Capacity Following Operation, *Surg., Gynec. & Obst.* **44**:483, 1927. (d) Beecher, Henry K.: The Measured Effect of Laparotomy on the Respiration, *J. Clin. Investigation* **12**:639 (July) 1933. (e) Carlson, Herbert A.: Inhibition of Respiration as a Factor in the Pathogenesis of Post-Operative Pulmonary Complications, *J. Thoracic Surg.* **2**:196, 1932. (f) Allen, K. D. A.: Post-Operative Behaviour of the Diaphragm, *Radiology* **16**:492 (April) 1931. (g) Breuer, F.: Ueber einseitige postoperative Zwerchfellschädigung, *Arch. f. klin. Chir.* **161**:443, 1930. (h) Klotz, L., and Straaten, T.: Postoperative Hypoventilation der Lungen, *Klin. Wchnschr.* **10**:1952 (Oct. 17) 1931.

5. Elliott, T. R., and Dingley, L. A.: Massive Collapse of Lungs After Surgical Operations, *Lancet* **1**:1305, 1914. Coryllos, P. N., and Birnbaum, G. L.: Obstructive Massive Atelectasis of the Lung, *Arch. Surg.* **16**:501 (Feb.) 1928.

6. Van Allen, C. M., and Lindskog, G. E.: Obstructive Pulmonary Atelectasis: Problems of Pathogenesis and Clinical Management, *Arch. Surg.* **21**:1195 (Dec.) 1930.

is common in conditions involving the upper part of the abdomen allowed time for an adequate preoperative examination. A history was taken, with particular attention to respiratory and cardiac illnesses and to colds, sinusitis and dental or gingival infections. The physical examination was made with especial attention to the thorax and thoracic organs. Roentgenograms were made with the patient in bed in a position similar to that to be assumed after operation.<sup>7</sup> The technic was such<sup>8</sup> that the tube-plate distance, the length of exposure and the direction of the rays were standardized and thus allowed comparison of successive roentgenograms. The physical and roentgenographic examinations were repeated every two to four days after operation for a period of two weeks, or until no further changes were noted.

*Symptoms and Physical Findings.*—The clinical data for the whole group of patients are summarized in table 1. Except for one appendectomy the operations were performed on the upper part of the abdomen. The anesthetic employed was ether alone or ether preceded by nitrous oxide and oxygen, with the exception of one case in which avertin was administered rectally. Unless otherwise stated all the abnormal symptoms and physical signs appeared within four days after the operation. Most of the symptoms were observed on the second or third postoperative day.

Symptoms referable to respiratory disease were usually of slight degree, such as cough, sputum, fever or a feeling of "catching cold."

In six patients cough developed; in four the cough was productive. A postoperative rise in temperature, for which the operation itself may have been partly responsible, was present in all and varied considerably in duration. It is noteworthy that in five instances the patient described the subjective symptoms during his postoperative course as similar to those accompanying "catching cold." This did not refer to the characteristic symptoms of coryza, which could not be found on examination of the nose and pharynx, but probably had to do with irritation of the nose and throat and with general malaise. Striking symptoms usually associated with pneumonia were rare. Pain in the chest was noted in only one case eight days after operation and gave rise to the diagnosis in infarction of the lung. Cyanosis was present in one severe case of bronchopneumonia. Chills did not occur in any case.

In contrast to symptoms, physical signs of pulmonary changes were present in all the patients in varying combinations and in varying degree. They ranged from an elevation of the diaphragm with corresponding physical signs to signs of a well marked collapse of a lobe or of a well

7. A portable roentgenographic apparatus was used for this purpose by one of us (B. F. S.) through the courtesy of Dr. P. F. Butler, radiologist to the Boston City Hospital.

8. Steele, Brandt F.: To be published.

defined bronchopneumonia. Elevation of the diaphragm was the most constant change, appearing postoperatively in all the patients. It was best recognized and measured in roentgenograms. It gave rise to dulness and scattered transient râles at the bases of the lungs posteriorly. In addition to signs readily ascribed to the elevated position of the diaphragm, other signs of pulmonary changes were frequently present. Râles were found in nine cases, dulness in six, diminished breath sounds in four and bronchial breathing in six. Patchy roentgenographic shadows appeared postoperatively in six cases and diffuse haziness of the lung in three. A similar high incidence of physical signs of pulmonary and diaphragmatic changes has been noted by other observers following operations on the upper part of the abdomen.<sup>9</sup>

*Diagnosis.*—A diagnosis of the thoracic condition was readily made in certain cases (table 1). In four cases nothing more than an elevation of the diaphragm with corresponding physical signs was observed (cases 1, 2, 3 and 13). These patients were said to have "hypoventilation," after the suggestion of Muller, Overholt and Pendergrass.<sup>10</sup> They represent the group with the minimum of postoperative pulmonary changes observed in the whole series of sixteen patients. In two other cases outspoken symptoms and signs of pulmonary complications were noted: lobar collapse in case 7 and bronchopneumonia in case 10. These two cases represent the maximum of postoperative changes observed. It is possible that only cases of maximum severity, such as the latter two, have been noted by observers who have determined the incidence of postoperative pulmonary complications. Two cases out of a total of sixteen represent only a slightly greater frequency than the 10 per cent quoted as the usual incidence. Owing to close observation in the present series, however, definite roentgenologic evidence and physical signs of less severe respiratory complications were found in nine other patients. Two of them had a mild bronchitis, one had a collapse, two had a combination of collapse and bronchopneumonia and one had a combination of infarction and bronchopneumonia. The diagnosis was more difficult in four of the cases. Three of these were finally called bronchopneumonia because of the physical findings listed in table 1 (cases 12, 14 and 15). Thus the incidence of postoperative pulmonary complications was eleven out of sixteen, or 69 per cent.

The fourth patient (case 16), who showed a persistent fever, elevation and fixation of the right half of the diaphragm and obliteration of the right costophrenic sinus, probably had subphrenic peritonitis due to escape of bile or other material at operation.

9. Overholt, Richard H., and Veal, J. Ross: The Incidence, Character and Significance of Abnormal Physical Signs in the Chest Occurring After Major Surgical Operations, *New England J. Med.* 208:242 (Feb. 2) 1933.

TABLE 1.—Summary of Clinical Data

Patient	Operation	Anesthesia	Symptoms	Physical Signs	Lungs	Diaphragm Elevation, Cm.		Comment
						Right	Left	
						2.5	1.0	
1 J. T.	Cholecystotomy	Nitrous oxide and oxygen, ether	Fever (3 days)	Diminished breath sounds and few scattered râles at bases	Clear	2.5	1.0	Hypoventilation
2 H. M.	Cholecystectomy	Nitrous oxide and oxygen, ether	Fever (5 days)	Few transient scattered râles at bases	Clear	2.0	2.0	Hypoventilation Frequent colds; sore throat
3 M. D.	Colostomy	Ether	Fever (5 days)	Diminished breath sounds at bases	Clear	5.0	3.0	Hypoventilation
4 E. F.	Exploratory laparotomy	Nitrous oxide and oxygen, ether	Fever (10 days); cough; caught cold	Scattered râles throughout lungs	Clear	6.0	3.0	Bronchitis
5 M. McL.	Cholecystogastrotomy	Ether	Fever (19 days); caught cold; cough; sputum	Scattered râles throughout lungs	Clear	6.0	3.0	Bronchitis
6 M. D. R.	Cholecystotomy	Nitrous oxide and oxygen, ether	Fever (3 days)	Left side of thorax decreased in size; left side of thorax, dullness, diminished breath sounds	Left side of chest diffusely clouded; mediastinum slightly to left	7.0	6.0	Collapse of left lung
7 T. J.	Cholecystotomy	Nitrous oxide and oxygen, ether	Fever (5 days); asthmatic dyspnea	Dullness, diminished breath sounds in right lung, coarse râles and wheezes	Shadow in lower lobe of right lung; mediastinum to right	6.0	4.0	Collapse of right lung Chronic bronchitis and bronchiectasis; asthma 2½ years; peptic ulcer
8 M. C.	Colostomy	Nitrous oxide and oxygen, ether	Fever (15 days); cough and sputum increased	Dullness, râles, bronchial breath and voice sounds, right side of chest posteriorly	Diffuse mottled areas and patchy shadows	2.0	4.0 (depressed)	Chronic bronchitis, increased 3 mos.; died 15 days after operation; autopsy showed resolving bronchopneumonia, carcinoma of lungs, carcinoma of splenic flexure, beta hemolytic streptococci septicaemia

9 O. P.	Exploratory laparotomy	Nitrous oxide and oxygen, ether	Fever (22 days); pain in right costal margin	Dullness, diminished and bronchial breath sounds, bases of right and left lung	Patchy shadows in lower part of chest, right and left	8.0	6.0	Infarction, bronchopneumonia	Cold 2 weeks before operation; none in hospital; carcinoma of stomach with metastases
10 P. V.	Cholecystectomy	Ether	Fever (5 days)	Bronchial voice and breath sounds; showers of fine crackling rales, both bases, more in right lung	Patchy shadows in lower part of chest, right and left	6.0	?	Bronchopneumonia	Chronic bronchitis 15 years; died 6 days after operation; no autopsy
11 A. B.	Partial gastrectomy	Averth, nitrous oxide and ether	Fever (4 days); caught cold; cough; sputum	Dullness, bronchial breath sounds, medium moist rales posteriorly in right side of chest	Patchy shadows, diffuse shadow in right side of chest	5.0	5.0	Collapse of right lung; bronchopneumonia right lung	Frequent colds
12 N. F.	Cholecystectomy	Nitrous oxide and oxygen, ether	Fever (9 days)	Dullness, increased voice sounds, showers of fine rales at base of right lung near spine	Small shadow in lower part of chest, right	6.0	4.0	Bronchopneumonia	Slight cough for 1 week before operation
13 E. P.	Cholecystectomy	Ether	Fever (12 days); caught cold	Diminished breath and voice sounds in right side of chest	Clear; thoracic scoliosis to right	3.0	?	Hypoventilation	Clinical course suggested pulmonary complication
14 R. S.	Appendectomy	Ether	Fever (5 days); caught cold	Bronchial breath sounds and rales at base of right lung	Clear	2.0	2.0	Bronchopneumonia	Frequent colds for 5 mos. before operation; last 3 days before operation
15 A. H.	Cholecystectomy	Ether	Fever (4 days); slight cough; sputum	Bronchial breath sounds and rales in showers at base of right lung posteriorly	Clear	7.0	4.0	Bronchopneumonia	Chronic sinusitis; pyorrhea
16 F. W.	Cholecystectomy; repair of common duct	Ether	Fever (25 days)	None	Lung clear; right side of diaphragm high, fixed; costophrenic sinus obliterated	10.0	6.0	Subphrenic abscess, bile? foreign body?	Chronic cough and sinusitis 15 years; purpura postoperatively



## REPORT OF CASES

The following report of cases gives the complete description of four cases in which pulmonary findings were characteristic and relatively unmodified by unrelated conditions.

**CASE 10.—History.**—P. V., a man, aged 46, entered the hospital complaining of intermittent pain in the right upper abdominal quadrant and vomiting. He had had a chronic productive cough for thirteen years. Physical examination revealed dental caries, oral sepsis, slight inflammation of the pharynx and numerous fine moist râles in the bases of the lungs posteriorly. Roentgenograms showed prominent trunk markings toward the bases but were otherwise negative.

A diagnosis of cholecystitis was made. Cholecystectomy was performed under ether anesthesia, lasting one and a half hours. Induction of anesthesia was difficult owing to marked excitement. The patient's respirations were irregular, and he was slightly cyanotic.

**Postoperative Course.**—On the first postoperative day the temperature rose to 101.4 F., and the pulse rate was 136. The patient was unable to cough because of pain in the wound. Moderate distention was present. The breath sounds were loud and harsh anteriorly and in the right side of the chest posteriorly. A roentgenogram showed patchy shadows at the bases of both lungs. The diaphragm was elevated 6 cm. on the right and 5 cm. on the left. On the second day the distention was more severe. Bronchial voice and breath sounds were heard at the bases of both lungs, and medium-sized and fine moist râles were heard throughout the chest. By the fourth day the respiratory rate had risen to 40. The physical signs remained the same. The cough was productive of a thick purulent sputum. Roentgenograms showed extensive patchy shadows at the bases of both lungs. On the fifth day the temperature was 101.6 F., the pulse rate 130 and the respiratory rate 40. Breathing was labored and grunting, and distention was marked. Cyanosis appeared. Dulness, râles and bronchial breath sounds were present at the bases of both lungs. On the evening of the fifth day the temperature, pulse rate and respiratory rate rose rapidly, and the patient died. Permission for autopsy was not obtained.

**Bacteriologic Observations.**—A pneumococcus of type XVII was cultured from the pharynx before operation and again on the third day postoperatively. On the fourth day pneumococci of type III were cultured in large numbers from the sputum and pharynx. Blood cultures on the fourth and fifth days were negative.

**Comment.**—In this patient severe bilateral bronchopneumonia developed on the third day after operation and led to death on the fifth day after operation. Chronic bronchitis and oral sepsis were probably significant predisposing factors. The progress of the surgical condition was also stormy. The type III pneumococcus first appeared and predominated in the sputum and pharynx coincidentally with the appearance of pneumonia.

**CASE 11.—History.**—A. B., a white widow, aged 66, entered the hospital complaining of chronic gastric distress. A diagnosis of operable carcinoma of the stomach was made. The patient was subject to frequent slight colds and had had one attack of bronchitis three years before admission. Physical examination showed that the lungs were clear and the mouth and throat normal.

A partial gastrectomy was performed under rectal administration of avertin as a basic anesthesia, with nitrous oxide and oxygen for one hour and a small amount of ether for ten minutes. The operation lasted two hours and fifteen minutes.

*Postoperative Course.*—The patient felt quite comfortable for the first two postoperative days. The right half of the diaphragm was elevated 5.5 cm., the left 4 cm.; both sides were mobile. A few scattered râles were heard at the bases of both lungs posteriorly. On the third day the patient felt as though she had "caught cold," and coughed up thick, glairy, grayish sputum. The temperature, which had dropped to near normal, rose to 103.8 F. and the pulse rate to 120. The breath sounds were harsh, and a few râles were heard in the bases posteriorly. On the fourth day the physical signs were the same, but a roentgenogram showed patchy shadows in the bases of both lungs and a diffuse clouding of the entire right side of the chest. The temperature and pulse rate returned to normal. On the following day, in addition to the râles, dulness and harsh breath sounds with a bronchial quality were noted at the base of the right lung posteriorly. The cough, sputum, physical signs and roentgenographic shadows gradually disappeared, and the patient had recovered from the pulmonary complication by the tenth postoperative day. She was discharged on the twenty-second postoperative day with the surgical condition improved.

*Bacteriologic Observations.*—No respiratory pathogens were cultured from the pharynx before operation or on the first postoperative day. A pneumococcus of type XXXI was cultured from both the pharyngeal swab and sputum on the third day, from the sputum on the fourth day and from the pharynx on the twelfth and fifteenth days. No pneumococci were found on the seventh and eighteenth days or on two occasions six weeks and five months after operation.

*Comment.*—The respiratory symptoms of postoperative pulmonary collapse and bronchopneumonia were remarkably slight, and the physical signs were much less than might have been expected from observation of the roentgenograms. A pneumococcus appeared in the sputum and pharynx coincidentally with the postoperative pulmonary complication.

*CASE 6.—History.*—M. Di R., an Italian woman, aged 37, was admitted with a story of severe abdominal pain, nausea, vomiting, poor appetite and jaundice for one month. Moderate tenderness and voluntary spasm were found in the right upper quadrant of the abdomen.

*Physical Examination.*—The patient was moderately obese and did not appear acutely ill. Her incisor and canine teeth were quite carious, and pyorrhea was marked. The examination of the chest showed no abnormal findings.

*Operation.*—Cholecystectomy was performed, revealing acute subsiding cholecystitis and cholelithiasis. A transduodenal incision into the ampulla of Vater was made for removal of a large irregular stone. Nitrous oxide and oxygen were used for the induction of anesthesia and were followed by ether, of which 11 ounces (342.14 Gm.) was used. The anesthesia lasted forty minutes, and the operation thirty-three minutes. The course of the anesthesia and operation was uneventful.

*Postoperative Course.*—On the first day after operation the patient complained of abdominal pain; the temperature rose to 102 F. and the pulse rate to 120. Roentgenograms showed diffuse clouding of the left side of the chest with narrowing of the left intercostal spaces and bilateral elevation of the diaphragm. On the second day a relatively smaller size and decrease in the breath sounds in the left side of the chest were noted. On the third postoperative day the mediastinum was seen at the left of the midline in a roentgenogram taken at the height of inspiration. Gastro-intestinal complaints were not present after the third day. The temperature and pulse rate decreased gradually and were normal on the twelfth postoperative day, and the physical signs and roentgenologic changes dis-

appeared at about the same time. The patient was discharged from the hospital on the seventeenth day after operation.

*Bacteriologic Observations.*—A pneumococcus of type XIV was found in one of two preoperative and in five of six postoperative specimens.

*Comment.*—The diagnosis of collapse of the left lung was obvious in this case, and there was apparently no bronchopneumonia. The postoperative course, with the exception of the physical findings, was not such as to arouse suspicion of a pulmonary complication. A pneumococcus of type XIV was persistently present in the pharynx.

*CASE 3.—History.*—M. D., an Irish housewife, aged 52, was admitted to the hospital on Feb. 15, 1933, complaining of abdominal cramps and pain for two months accompanied on one occasion by a shaking chill.

In the past the patient had had frequent colds with sore throats and hoarseness. These ceased two years before admission. During the present illness of two months the hoarseness reappeared occasionally.

*Physical Examination.*—The tonsils were slightly large but not inflamed. The right anterior faucial pillar was quite red. No teeth other than two carious lower canines and four lower incisors were present. All these were surrounded by pyorrheic gums. The heart was moderately enlarged, the apex being 12 cm. to the left in the fifth space. A soft blowing systolic murmur was present at the apex.

*Operation.*—An exploratory laparotomy and cecostomy were performed. A mass was palpated in the sigmoid colon, and multiple metastases were found in the peritoneal coats of the intestines and lymph glands. Ether was used as the anesthetic; 7 ounces (217.7 Gm.) was required during sixty minutes. During the anesthesia the pulse rate rose gradually from 80 to 120 and the respiratory rate rose to 52 in the first ten minutes, remaining about 50 until the close of the operation when it fell to 38. The operation lasted forty-five minutes. The cecostomy was performed forty-eight hours after the initial operation.

*Postoperative Course.*—During the first twenty-four hours after operation severe gas pains and slight distention were present; the breath sounds were fainter than normal in the right side of the chest; the temperature was 100 F. and the pulse rate 104. The results of roentgenologic examination were negative, except for marked elevation of the right side of the diaphragm and slight elevation of the left. Indigestion persisted for six days, the diminished respiration in the right side of the chest for seven days, the elevation in temperature for four days and the increase in pulse rate for one day. The diaphragm resumed its normal position on the fourteenth postoperative day. The patient was discharged on the twenty-first postoperative day unimproved.

*Bacteriologic Observations.*—No pneumococci were found in the sputum on three preoperative and on four postoperative examinations.

*Comment.*—The only noteworthy findings were the elevation of the right side of the diaphragm and the diminished breath sounds. A diagnosis of hypoventilation was made. No respiratory pathogens were found.

These four cases illustrate pulmonary complications that are relatively common after operations on the upper part of the abdomen. They range from conditions that may be considered as physiologic alterations to definite pathologic changes and include variations between

these extremes. During the progress of this work other pulmonary complications were observed in patients who were not studied before operation. These included lobar pneumonia, pulmonary abscess, encapsulated pleural effusion, collapse of a lobe of the lung with explosive onset, acute infection of the lung with organisms of the *Bacillus Welchii* group, pulmonary embolism and localized edema of the lung associated with carcinomatosis and phrenic exeresis. Such conditions are relatively infrequent and depend on the presence of unusual circumstances. The present report is confined to the milder changes that occur in some degree following most or all operations on the upper part of the abdomen and the most common pulmonary complications.

#### BACTERIOLOGIC OBSERVATIONS

*Methods.*—Repeated examinations of the pharyngeal flora were made, in the majority of cases on three occasions before operation and at intervals of from one to four days postoperatively. A cotton swab was passed over the nasopharynx and tonsils and placed in 5 cc. of dextrose blood broth which was shaken vigorously. The broth was cultured at once on the surface of poured blood agar plates. The broth and swab were incubated at 37 C. for two hours, and 0.5 cc. was injected into the peritoneal cavity of a white mouse. Respiratory pathogens were isolated in pure culture for identification. The serologic type of each strain of pneumococcus was determined by means of agglutinating serums specific for thirty-one types.<sup>10</sup>

*Results of Bacteriologic Examinations.*—A summary of the organisms isolated from the pharyngeal secretions and sputums in the sixteen cases studied clinically is given in table 2. The respiratory pathogens most frequently found were various types of pneumococci. Other significant organisms were the beta hemolytic streptococcus, Friedländer's bacillus (*Encapsulatus pneumoniae*) and a nonspecific, mouse-virulent alpha hemolytic streptococcus. Table 2 also shows the relationship between the presence of these respiratory pathogens and the occurrence of pulmonary complications.

In regard to the presence of respiratory pathogens three groups of cases may be distinguished:

1. One group (cases 1, 2 and 3) which showed no pneumococcus at any time. These patients all manifested the minimum of postoperative pulmonary changes, called hypoventilation.

10. Cooper, G.; Edwards, M., and Rosenstein, C.: The Separation of Types Among the Pneumococci Hitherto Called Group IV and the Development of Therapeutic Subserums for These Types, *J. Exper. Med.* 49:461, 1929. Cooper, G.; Rosenstein, C.; Walter, A., and Peizer, L.: Further Separation of Types Among Pneumococci Hitherto Included in Group IV and Development of Therapeutic Antisera for These Types, *J. Exper. Med.* 55:531, 1932.

2. Six cases which showed a pneumococcus or beta hemolytic streptococcus constantly or intermittently, but with no relationship to a pulmonary complication. A diagnosis of pulmonary complication was made in each of these cases; bronchitis in cases 4 and 5, collapse in cases 6 and 7, collapse associated with bronchopneumonia in case 8 and infarction and bronchopneumonia in case 9.

TABLE 2.—*Summary of Bacteriologic Data*

Group	Patient	Respiratory Pathogens		Diagnosis
		Preoperatively	Postoperatively	
Cases with no respiratory pathogens in pharynx	1. J. T.....	None	None	Hypoventilation
	2. H. M.....	None	None	Hypoventilation
	3. M. D.....	None	None	Hypoventilation
Cases with respiratory pathogens in pharynx not related to post-operative course	4. E. F.....	Pneumococcus type XXI	Pneumococcus type XXI, type XIX-XXIX	Bronchitis
	5. M. McL....	Pneumococcus type III, beta hemolytic streptococcus	Pneumococcus type XXI, beta hemolytic streptococcus	Bronchitis
	6. M. Di R....	Pneumococcus type XIV	Pneumococcus type XIV	Collapse of left lung
	7. T. J.....	Pneumococcus type XXVIII, type XXIII	Pneumococcus type XXIII	Collapse of right lung
	8. M. O.....	Pneumococcus type III	Pneumococcus type III	Collapse of right lung, bronchopneumonia
	9. C. P.....	Pneumococcus type XXIX, beta hemolytic streptococcus	Pneumococcus untyped, beta hemolytic streptococcus	Infarction of lung, bronchopneumonia
	10. P. V.....	Pneumococcus type XVII	Pneumococcus type XVII, type III	Bronchopneumonia
	11. A. B.....	None	Pneumococcus type XXXI	Collapse of right lung, bronchopneumonia
	12. N. F.....	None	Pneumococcus type VI, type XIV, type XVI	Bronchopneumonia
Cases with respiratory pathogens in pharynx related to postoperative course	13. E. P.....	Pneumococcus type XIII	Pneumococcus type XX	Hypoventilation
	14. R. S.....	None	Pneumococcus type XX	Bronchopneumonia
	15. A. H.....	None	Alpha hemolytic streptococcus (mouse-virulent)	Bronchopneumonia
	16. F. W.....	Bacillus mucosus-capsulatus	Pneumococcus type XIX, B. mucosus-capsulatus	Subphrenic abscess

3. A group of seven cases in which a pneumococcus or, in one instance, a mouse-virulent alpha hemolytic streptococcus was found after operation coincidentally with pulmonary changes. In two of these a second type of pneumococcus was present either before or both before and after operation, and in a third a Friedländer bacillus was present throughout the course in the hospital. In the remaining four cases the organisms that appeared postoperatively were the only respiratory pathogens found.

Bronchopneumonia was present in five cases of this group; severe pneumococcus type III pneumonia that proved fatal occurred in case 10; bronchopneumonia associated with collapse, in case 11, and quite mild bronchopneumonia, in cases 12, 14 and 15. Hypoventilation was present in case 13, and a subphrenic bile peritonitis was present in case 16.

The presence of pathogenic bacteria in the upper respiratory tract is related in several ways to the postoperative clinical course. Patients without pathogenic bacteria had hypoventilation but no other evidence of pulmonary involvement, while most patients with pathogenic bacteria had signs and symptoms of pulmonary involvement other than hypoventilation. The latter group includes one patient with severe bronchopneumonia due to type III pneumococci. The conclusion may readily be drawn that the pulmonary signs were the result of the presence of the micro-organisms, and the severity of the pulmonary lesion was proportional to the virulence of such organisms.

Other interesting aspects of the bacteriologic observations require comment. Case 5, in which the type III pneumococcus was present constantly in the pharynx may be compared with case 10 in which a fatal type III bronchopneumonia occurred. In the former the general postoperative reaction was slight, and the patient's temperament was such that he did not rest quietly in bed longer than he was forced to by the anesthetic and medications. In the latter patient abdominal pain and distention were evident after operation, with a resulting limitation of changes in position and of respiratory excursions. He also had a marked chronic bronchitis with purulent sputum. The type III pneumococcus was not found before operation but appeared after operation at the onset of definite pneumonia. The modifying influence of bronchial drainage, assisted by frequent changes in position, on the severity of postoperative complications in the presence of virulent organisms is suggested by this comparison. The preexisting infection in the bronchi and lung may have been an important deleterious influence in the case in which bronchopneumonia developed.

In tables 1 and 2 a general relationship may be observed between the presence of respiratory pathogens and chronic infection of the upper respiratory tract, and to a lesser extent between these organisms and recent acute infection of the upper respiratory tract. There is also a similar association between the presence of chronic nasopharyngeal and bronchial infection and postoperative pulmonary signs and symptoms.

Patients with collapse of portions of the lung are included among those from whom pneumococci or other pathogens were obtained. In the most severe case of collapse, case 7, a chronic bronchitis with some asthmatic manifestations was noted before operation. In this patient the connection between the chronic infection and the appearance of lobar collapse of the lung due to plugging of a bronchus is apparent.

Metastatic carcinoma of the lungs was an important complication in three cases. In case 9 the primary carcinoma was in the splenic flexure of the colon. This patient had signs of bronchopneumonia in the right side of the chest which were evident only when he lay on his left side and which disappeared when the right side of the chest was dependent. Successive roentgenograms showed first shadows at the bases of both lungs, later diffuse mottling of both pulmonary fields, and before death partial clearing of both pulmonary fields. At autopsy gross examination showed chiefly congestion of the lungs, but microscopic examination showed diffuse patches of bronchopneumonia and widely disseminated collections of tumor cells in pulmonary lymphatics. *Streptococcus haemolyticus* was recovered from the blood stream. In another patient, not included in this series of sixteen, who had carcinoma of the stomach, the physical signs of lobar pneumonia appeared at the base of the right lung following right phrenic exeresis and exploratory laparotomy. Autopsy showed a firm, relatively bloodless sharply localized area of edema at the base of the right lung. Microscopic examination confirmed the presence of marked edema and showed small collections of tumor cells throughout the lymphatics of both lungs. In a third patient (case 8) with carcinoma of the stomach bilateral bronchopneumonia developed after operation. He was discharged against advice on the twenty-second postoperative day with persisting pulmonary infiltration. In the two cases that came to autopsy the microscopic lymphatic pulmonary metastases may have been in part responsible for the *Streptococcus haemolyticus* bronchopneumonia with bizarre signs in one and for the localized edema in the other. A similar condition may have been responsible for the persisting signs in the third case. Patients operated on for carcinoma of the stomach or of the upper part of the colon must be considered as a special group in regard to the development of pulmonary complications.

If the nasopharyngeal pathogenic micro-organisms had regularly been found before operation the course of events would be much clearer. Autogenous infection probably through aspiration could be assumed. But in seven of these cases the pathogenic micro-organisms appeared in the pharynx or sputum coincidentally with the signs of pulmonary disturbance. Repeated examinations before operation by a technic designed to isolate even small numbers of relatively avirulent pneumococci insure that they were absent from the pharynx at the time or hidden in inaccessible parts of the upper respiratory tract. The number of cases in which new organisms appeared indicates that it was not a coincidental observation due to the normal shifting of pneumococcal strains. The relationship of this observation to the pathogenesis of the pulmonary complications and the source of the organisms will be discussed later.

## COMMENT

The high incidence of physical signs and roentgenographic changes observed by frequent examinations of lungs and thorax in this group of sixteen cases is not surprising in view of the similar findings of Muller, Overholt and Pendergrass,<sup>4a</sup> and of Overholt and Veal.<sup>9</sup> The frequency of pulmonary changes following operations on the upper part of the abdomen has also been shown through studies on vital capacity,<sup>11</sup> through studies of the volume of air spaces in the position at the end of tidal expiration,<sup>4d</sup> through studies of the respiratory movements<sup>4e</sup> and through studies of the postoperative elevation of the diaphragm.<sup>12</sup>

The interpretation of the nature of these changes is obvious in cases in which the physical signs were clearly those of an elevated position of the diaphragm or of other limitation of respiratory movements. It was also obvious in cases that presented clearcut evidence of changes such as collapse or bronchopneumonia. In some of the cases, however, the signs were slight and transient. They might have been due to compression of the lung alone, to circulatory changes in the lungs, to excessive bronchial secretion, to aspiration of oral and pharyngeal secretions, to bronchial obstruction and collapse or to infection. It is possible that all these factors are active in varying degrees at different times. In this study the pulmonary changes have been named according to the conventional terminology, bronchitis, collapse or bronchopneumonia, implying the presence of certain of these factors. It is believed that approximate justice has thus been done to all the factors listed, with the possible exception of circulatory changes about which little information is available.

The pathogenic micro-organisms found in the pharynges and sputums of the patients in this series were those which one would expect in any group of normal persons, with the exception of the postoperative appearance of new strains. Several investigators have determined that pneumococci are found in the throats of one half of normal persons on a single examination, and as the number of examinations and the period of time over which they extend are increased, the proportion found to harbor pneumococci is also increased to nearly 100 per cent.<sup>13</sup> Some persons carry pneumococci persistently, others

---

11. Powers.<sup>4b</sup> Churchill and McNeill.<sup>4c</sup>

12. Allen.<sup>4f</sup> Breuer.<sup>4g</sup> Klotz and Straaten.<sup>4h</sup>

13. Dochez, A. R., and Avery, O. T.: The Occurrence of Carriers of Disease Producing Types of *Pneumococcus*, *J. Exper. Med.* **22**:105, 1915. Powell, J. P.; Atwater, R. M., and Felton, L. D.: *Pneumococcus Carriers Among Four Groups of Persons Over a Period of Months*, *Am. J. Hyg.* **6**:570 (July) 1926. Gundel, M., and Linden, H.: *Die Flora der Mundhöhle Gesunder und ihre Bedeutung für die pathogene Erkrankungen der Athmungsorgane*, *Zentralbl. f. Bakt.* (Abt. 1) **121**:349, 1931.



only at intervals and a few very rarely.<sup>14</sup> More than one strain may be present at one time, and changes in the strain that is present occur frequently. Other organisms, such as beta hemolytic streptococci and Friedländer's bacillus, are less often present.

The significance of the observation of pulmonary changes and pharyngeal flora in the present series of cases after operations on the upper part of the abdomen lies in the apparent relationship between the two. Patients who had no respiratory pathogens in the pharynx had the least pulmonary changes, and those who harbored such organisms showed thoracic signs of varying degrees. A further relationship between the pharyngeal flora and the postoperative pulmonary changes consists in the simultaneous appearance of postoperative pulmonary changes and a given strain of pneumococci that was not found pre-operatively. Although such relationships have not been shown in any previous studies on postoperative pulmonary complications, no data have been reported that can be interpreted as contradictory. Whipple<sup>3a</sup> and Cleveland,<sup>3b</sup> working with a similar plan, but without the advantage of ready prepared serum for many specific strains of pneumococci, found that in a few patients there developed specific antibodies for a strain of pneumococci present before and after operation, but in the greater number of their cases there developed antibodies specific for a pneumococcus present only postoperatively. Moreover, their cultural results as a whole showed a greater frequency of pneumococci in the pharynx after operation than before. In regard to the organisms present in the lesion, the observations of Whipple<sup>3a</sup> at autopsy in seven cases and those of Gundel<sup>3c</sup> by pulmonary puncture in seventeen cases and at autopsy in thirty-four cases show the frequent presence of pneumococci. Such studies indicate the importance of pneumococci in well marked postoperative pulmonary lesions. The present data indicate a similar relationship in the milder, more frequent lesions.

The appearance after operation in slightly less than half of the cases of strains of pneumococci that were not present before operation brings up the question of their source. It is, of course, possible that they were present in the pharynx before operation, but in such small numbers or hidden so deeply in foci of infection that they were not found by the methods used. They may then have been mobilized by the secretions under narcotics or anesthesia, or they may have found conditions especially suitable for their proliferation. As alternative sources may be mentioned: (1) contact infection in the wards, and (2) mutation from rudimentary or rough forms of the same organism.

---

14. Webster, L. T., and Hughes, T. P.: Incidence and Spread of Pneumococci in Nasal Passages and Throats of Healthy Persons, *J. Exper. Med.* 52:535 (April) 1931.

From these observations it is apparent that infection by organisms common in the nose and throat is of importance in postoperative pulmonary complications. Changes in the physiology of respiration and circulation following operation are probably related to bronchitis, bronchopneumonia and collapse to the degree that they favor the penetration of micro-organisms in the lower respiratory tract and interfere with their subsequent disposal. An understanding of such relationships is necessary for the development of prophylaxis and therapy based on physiologic procedures. Measures directed against the invading micro-organism may also be considered. The study of the respiratory flora, its virulence and the immune reactions of the patient may point out certain patients who are particularly liable to severe infections. In certain circumstances, the use of immunizing methods based on procedures such as those developed by Felton<sup>15</sup> and Ross<sup>16</sup> may be of value.

#### SUMMARY AND CONCLUSIONS

Sixteen cases were studied before and after abdominal operations with regard to the development of postoperative pulmonary complications and to the presence of respiratory pathogens in the pharynx and sputum. A high incidence (69 per cent) of pulmonary complications was found. Three patients without pathogenic organisms in the pharynx before or after operation had the least changes in the lungs. Of the remaining thirteen patients with pathogenic organisms in the pharynx, eleven had postoperative pulmonary changes greater than the minimum. In seven cases a strain of pneumococci not recovered before operation appeared postoperatively as part of the postoperative reaction.

The presence of relationships between postoperative pulmonary complications and the pharyngeal flora indicates an avenue of approach to the study of such complications that holds promise for the development of practical prophylactic methods.

Mrs. Mildred Barnes gave technical assistance in this investigation.

15. Felton, L. D.; Sutliff, W. D., and Steele, B. F.: Antigenic Characteristics in Man of Certain Products of the *Pneumococcus*: Comparison with Vaccine, *J. Infect. Dis.*, to be published.

16. Ross, V.: Oral Immunization Against the *Pneumococcus*, *J. Exper. Med.* 51:585 (April) 1930.

# SENILE OSTEOMALACIA

## REPORT OF A CASE

SAMUEL KLEINBERG, M.D.

NEW YORK

Porosity of bone is a frequent sequel in many pathologic states. It may be found in a single bone or in many bones in the same patient. It is, however, seldom a primary lesion causing local pain and deformity. The etiology of atrophy of bone is usually apparent, and can be classified readily under one of the following headings: (1) disuse, (2) neurogenic, (3) endocrinologic or (4) nutritional. The case reported here is unusual because: 1. The atrophy of bone was limited to the spinal column and pelvis. 2. The etiology was obscure. 3. The softening of the vertebral bodies resulted in a painful posterior curvature of the spine. 4. Rest on a convex frame yielded complete relief.

## REPORT OF A CASE

Mrs. Rose Y., 65 years old, was admitted to my service at the Israel Zion Hospital, Brooklyn, because of increasing pain and deformity of her back. She had been under observation in the dispensary for about two years. During this period the backache, which was not preceded by a known injury or illness, but began insidiously, continually increased in severity. At the same time her back became kyphotic and her height noticeably diminished. The symptoms finally reached a point at which the patient was practically totally incapacitated. The pain was in the lower dorsal region, and radiated to the left side of the abdomen.

Examination revealed an elderly, fairly well nourished woman, who stood and walked without assistance. She presented kyphosis of the spine, most marked at the dorsolumbar junction. There were flattening of the chest, prominence of the lower portion of the abdomen and a horizontal crease across the upper part of the abdomen indicative of fixed flexion of the spine. The movements of the spine were markedly restricted, and there was spasm in all the muscles of the back. Pressure over the spine, especially between the eighth dorsal and the second lumbar vertebrae elicited marked tenderness. There were periarticular thickening in the fingers and moderate limitation of the motions of the shoulders. The physical examination revealed no other abnormalities.

Roentgenograms showed extensive pathologic change in the vertebrae and pelvis, but none in the skull or extremities.

The most conspicuous change was severe atrophy of the vertebrae (fig. 1), most marked in the dorsal region, with deformity of certain of the dorsal bodies. There was a short curvature to the left at the dorsolumbar junction and to the right in the midlumbar and lower lumbar areas. There was wedging of the vertebrae involved in the curvatures. The seventh, ninth and eleventh dorsal vertebrae were markedly reduced in their vertical diameters. The first lumbar

vertebra was misshapen. The outlines of all the vertebrae, except those at the dorsolumbar junction, were clearly visible, but there was marked thinning of the cortical and cancellous bone. The intervertebral disks on both sides of the seventh and ninth dorsal vertebrae were increased in size and were biconvex. Between the tenth dorsal and the second lumbar vertebrae the disks were reduced in size



Fig. 1.—The general atrophy of all the vertebrae is notable. There are a slight compound lateral curvature, a marked reduction in the vertical diameter of the seventh and ninth dorsal vertebral bodies and a marked wedge deformity of the eleventh dorsal vertebra, with apparently complete disappearance of the intervertebral space between the eleventh dorsal and the first lumbar vertebrae.

and barely distinguishable. The lumbar articulations were clearly seen. There was no peripheral lipping.

The lateral view of the spine (fig. 2) showed the lesion most marked in the dorsal section, the lumbar vertebrae exhibiting practically normal conformation.

The seventh dorsal vertebra was compressed so that its vertical diameter was scarcely more than a fourth of normal size. The greatest compression was through the center. The borders of the body were distinct, but thin; the upper border was mildly concave, the lower border markedly so. The cancellous tissue was rarefied. The posterior arch and the spinous process had a denser consistency. The ninth

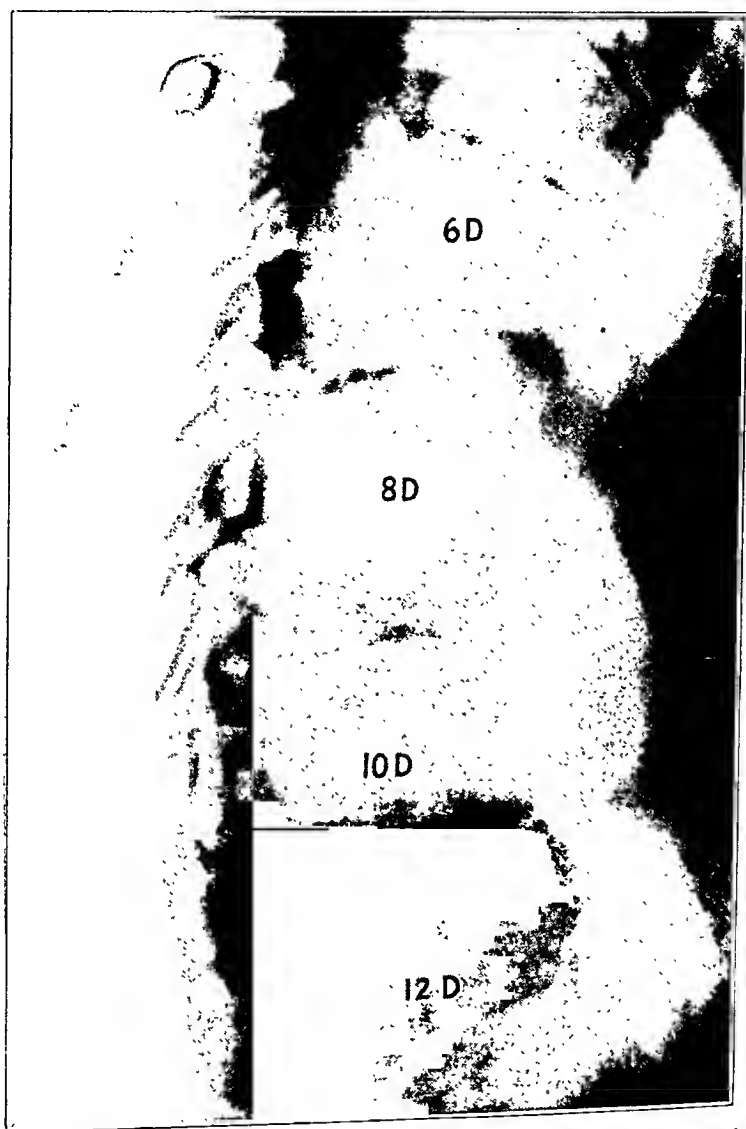


Fig. 2.—The osteoporosis is very evident, particularly as it affects the dorsal spine. Note the marked reduction in the vertical diameter of the seventh and ninth dorsal vertebrae and the biconvex character of the adjacent intervertebral disks. The eleventh dorsal vertebra is wedge-shaped, with almost complete disappearance of the anterior part of the body. The tenth and twelfth dorsal vertebrae are elongated in their anteroposterior diameters.

dorsal vertebra showed the same alteration in outline, size and density as the seventh dorsal. The eleventh dorsal showed a much more advanced lesion. The body was wedge-shaped, with the base posteriorly, and of about half the normal

height, with the apex in front, the anterior half of the body being reduced to a narrow amorphous mass. It appeared to be fused with the tenth dorsal vertebra. The texture of the bone was denser than that of the adjacent vertebrae. The tenth and twelfth dorsal vertebrae appeared to be elongated in their anteroposterior diameters, which were twice the length of the vertical diameters. The anterior borders of the bones were irregular. The sixth and eighth dorsal vertebrae were smaller than normal and greatly atrophied.

In the pelvis was extensive irregular rarefaction of the ischium and pubic bones on both sides, but without deformity.

The urine and blood were normal except for lymphocytosis. The blood calcium and phosphorus values were normal, and the test of the basal metabolism rate yielded a normal figure.

#### COMMENT

The most difficult problem in this case related to the etiology of the atrophy. A malignant process was evidently not responsible for the osseous changes, for (1) there was no primary focus anywhere in the body, (2) the lesion in the spine had existed for two years without impairment of the general health and without cachexia, and (3) the pain in the back was not as intense or as unyielding as that customarily experienced in a metastatic malignant process in the vertebrae. Hodgkin's disease was excluded by the blood cell picture. The normal values for blood calcium and phosphorus eliminated the possibility of tumor or disease of the parathyroid bodies, and the normal basal metabolic rate precluded dysfunction of the thyroid gland as a cause of the osseous pathologic process.

The clinical examination revealed no neurologic disturbances in the cerebrospinal system which could induce atrophy of bone.

Disuse as a basis for the osteoporosis may be dismissed from consideration, because the patient, despite the pain, was able to get about considerably, walking and working every day.

Thus, by a process of exclusion, my colleagues and I were compelled to conclude that the disease of the spine was nutritional or metabolic. The demineralization progressed to such a degree that it caused a partial collapse of certain of the dorsal vertebrae, with resultant pain and deformity. The nutritional upset may be considered a senescent degenerative change. Why the metabolic upheaval should appear and involve a limited portion of the skeleton is inexplicable.

#### TREATMENT

Though the etiology was obscure, the course of treatment that of necessity had to be pursued was readily apparent. The patient was put to bed on a canvas frame. Gradually, the frame was bent into a convex curve. This form of treatment immediately provided rest to the spine and freedom from the bearing of weight. As the curve of the frame

was increased the kyphosis of the spine was somewhat reduced. In addition, several times a day the patient received sedative doses of baking and massage of the back. The therapy was rapidly and surprisingly effective. Within three weeks the pain and tenderness disappeared, the kyphosis was reduced, and the patient, with the support of a light plaster of paris jacket, was able to move about comfortably and was discharged.

# PREOPERATIVE IRRADIATION OF MASSIVE TUMORS OF THE KIDNEY

A CLINICAL AND PATHOLOGIC STUDY

LAWRENCE R. WHARTON, M.D.

BALTIMORE

The object of this communication is to suggest for consideration a therapeutic measure which I have found helpful in facilitating the removal of large malignant tumors of the kidney. I refer to the use of preoperative high voltage roentgen therapy for the purpose of reducing the size of these enormous neoplasms. Although I feel sure that this adjunct of therapy is being introduced in some clinics, the literature as yet contains no specific report of it.

I cannot present a large series of cases, as, fortunately, a big renal tumor is not common. Also the effect that preoperative irradiation has on the chance of ultimate cure cannot be reported as this can be determined only with the passing of years. I shall, however, show the direct effect that irradiation has on the cytology and gross characteristics of these tumors and call attention to the immediate benefit of this treatment in making these tumors operable.

## PRESENT STATUS OF THE OPERATIVE PROCEDURE IN RENAL TUMORS

The treatment of renal tumors has always been unsatisfactory. Considering malignant renal growths of all types and sizes, Judd and Hand<sup>1</sup> reported in 1929 that not more than 10 per cent of their patients had lived as long as ten years after nephrectomy and that few had survived three. In children the prospect is even more unfavorable, as about 90 per cent die within a year after operation (Hyman,<sup>2</sup> Kretschmer and Hibbs,<sup>3</sup> Wollstein<sup>4</sup> Mixer<sup>5</sup>). The ultimate results are

---

From the Department of Gynecology, Johns Hopkins Medical School and Hospital.

Read before the Mid-Atlantic Section of the American Urological Association, Washington, D. C., Dec. 13, 1933.

1. Judd, E. S., and Hand, J. R.: Hypernephroma, *J. Urol.* **22**:10, 1929.
2. Hyman, A.: A Clinical Study of Malignant Tumors of the Kidney, *S. Clin. North America* **13**:347 (April) 1933.
3. Kretschmer, H. L., and Hibbs, W. G.: Mixed Tumors of the Kidney in Infancy and Childhood: Study of Seventeen Cases, *Surg., Gynec. & Obst.* **52**:1, 1931.
4. Wollstein, M.: Renal Neoplasms in Young Children, *Arch. Path.* **3**:1, 1927.
5. Mixer, C. G.: Malignant Tumors of the Kidney in Infancy and Childhood, *Ann. Surg.* **96**:1017, 1932.



therefore very unsatisfactory, and in children particularly, in whom large tumors are the rule, the outlook is practically hopeless.

After studying the collected experiences of various clinics, it seems to me that in the vast majority of instances, the failure to cure malignant tumors of the kidney is due to inability to remove the local growth completely. As a rule the disease is still localized when the surgeon operates. In general the history of these cases indicates that the tumor has been present for many months; in the largest reported series in this country, the average duration of preoperative symptoms had been two years. And yet none of these patients had any evidence of metastasis before operation. Too frequently after nephrectomy or exploration, however, there is a rapid local recurrence with a shower of distant metastases. Why is it so difficult to remove these tumors successfully?

Disregarding the important element of operative skill and experience, surgeons agree that the most serious technical difficulties are the size of the tumor, the thinness of the capsule, the extreme vascularity and friability of the mass, the invasion of perirenal structures, extension into the renal vein and the general condition of the patient. Surgeons encounter these handicaps usually in big tumors, for the risk in removing a small hypernephroma, no larger than an orange, is hardly greater than that in a nephrectomy for any other reason, probably not more than 5 per cent. But the mortality that accompanies the removal of massive tumors is so terrific that, even though large growths constitute less than half of the total number, the operative mortality of the whole group varies between 15 and 30 per cent.

Nor does this tell the whole story, for in every reported series a number of cases are found in which nephrectomy was attempted but abandoned because it proved to be too formidable a procedure. These cases are not included in the recorded instances of nephrectomy. The reports of Swan,<sup>6</sup> Hunt,<sup>7</sup> Wollstein<sup>4</sup> and others showed that the cases thus listed as instances of exploratory operations varied between 12 and 26 per cent. In 1933, Hyman<sup>2</sup> stated that the attempt to remove tumors which they formerly dared only to explore doubled their death rate. Furthermore, in another 5 or 10 per cent, no operation whatever was attempted because of metastasis or the extent of the local growth.

Not only is the size of the tumor the chief cause of this forbidding immediate mortality; it also definitely increases the number of local recurrences, in that many of these big tumors are broken during their removal, thus scattering bits of hypernephroma throughout the wound.

---

6. Swan, R. H. J.: *New Growths of the Kidney, with Analysis of Sixty-Five Cases*, Brit. M. J. **1**:606 (April 8) 1933.

7. Hunt, V. C.: *Factors of Importance in the Surgical Treatment of Malignant Renal Tumors*, Urol. & Cutan. Rev. **36**:291, 1932.

Thus, Judd and Hand<sup>1</sup> stated that in exactly one third of their three hundred and twelve nephrectomies for hypernephromas of all sizes, the capsule of the tumor was ruptured. The fact that practically all late deaths are due to a rapid local recurrence in the wound is sufficient evidence on this point. Also the excessive manipulation of large tumors during their removal favors metastasis, particularly when the renal vessels are not ligated early in the operation.

In general, then, of all patients who on presentation have had renal tumors, from 5 to 10 per cent have been refused any operative treatment because of metastasis or the extent of the local growth; from 12 to 26 per cent have had only exploratory operations; from 15 to 30 per cent have died of operative shock, and of the remainder, less than 10 per cent have been permanently cured.

With these experiences fresh in the memory of every one who has experienced the difficulty of removing large renal tumors or who has had occasion to review the literature, one is inclined to agree with Hyman<sup>2</sup> that "but little progress has been made in improving our percentage of cures."

Up to the present time, surgeons have been powerless in attacking these difficulties. It is true that they have learned the value of repeated transfusions of blood in building up the general condition of the patients, for this is now universal practice. Although it has probably saved some lives, its value is limited and its effect transitory because it may be rather difficult to accomplish much in restoring strength to a person who has an enormous malignant tumor and who is losing blood in the urine almost as fast as one dares to replace it by transfusion.

The one factor which has probably been responsible for more operative deaths than all others combined, the size of the tumor, has remained beyond control until the present time; now, however, in high voltage roentgen therapy, it is hoped that a means has been found of either eliminating or lessening this handicap. And it is my purpose to relate the experience of my associates and myself in trying to accomplish this result.

Roentgen therapy has been used in the treatment of renal tumors in several clinics, but almost exclusively after nephrectomy. Hunt,<sup>3</sup> in 1932, stated that "in extensive, well advanced lesions in which nephrectomy is contemplated, benefit probably occurs sufficiently often to justify preoperative and postoperative radiotherapy." He cited no specific instances, however, in which preoperative roentgen therapy was tried. In 1931 Kretschmer and Hibbs<sup>2</sup> reported a series of seventeen cases of Wilms' tumor in children, in one of which they used preoperative irradiation with some benefit. The child was operated on twice. At the first operation it did not seem possible that the tumor could be removed, and consequently, after a biopsy had been made, the

effort was abandoned. Roentgen treatments were then given which reduced the size of the tumor to such an extent that three and a half months later, nephrectomy was performed. Unfortunately, the child died four months afterward. Although postoperative irradiation was used rather frequently in this series, this was the only instance in which Kretschmer mentioned its use before operation. Neither Kretschmer nor Hunt seemed to find postoperative irradiation very beneficial.

My experience with preoperative irradiation has been striking. In the four cases in which I have used it, the enormous tumors seemed to shrink almost miraculously. And this decrease in size was usually accomplished within three weeks. Of my cases, two presented typical Grawitz hypernephromas, one in a girl of  $2\frac{1}{2}$  years, the other in a woman of 51; the other two growths were Wilms embryomas in children of 3 and 16 years. The rate and amount of decrease in the size of these tumors are shown in the illustrations.

By reducing the size of the tumor, the magnitude of the operation is greatly lessened. In addition, it is possible that this may diminish the likelihood of recurrence because the operation is made so much easier and can be done so much more cleanly. The smaller tumor can be removed with little manipulation or bleeding and with a much wider margin. It enables the surgeon to locate and tie the renal pedicle before disturbing the tumor, if the operation is done transperitoneally.

Furthermore when one examines a tumor which has been irradiated successfully, one cannot fail to be impressed by the extensiveness of the cellular destruction. Parts of the tumor consist of hyalinized tissue. In other areas the nuclei are small and pyknotic, the cells have lost their membranes, many have disintegrated, the architecture of the tumor has been destroyed and one gains the impression that the malignant process has been dealt a stunning blow. This is readily seen in the accompanying illustrations.

As will be pointed out, although irradiation may cause part of the tumor to melt away and may remarkably alter its morphology, the treatment does not destroy the tumor completely nor does it change its essential character, for the remaining part shows living malignant cells and prompt growth if it is not removed. Irradiation is therefore merely a useful adjunct in operative preparation, and cannot be expected to eliminate the malignancy. The tumor must be removed if the patient is to be cured.

#### OPERATION

*Preparation.*—With this experience, my associates and I have entirely changed our whole method of attacking these large neoplasms and also have revised our regimen of preparing the patient for the ordeal of nephrectomy. We now think that there is an excellent chance of bringing the patient through the operation successfully. It will be interesting to follow the subsequent course of these patients.

Our first object is to make the tumor operable by reducing its size through high voltage irradiation. Otherwise we know our chances are practically zero.

But even before irradiation is started, it may be necessary to give one or two transfusions, because the hematuria and toxemia may have produced a marked degree of anemia, hyperpyrexia and emaciation. If the large tumor has not affected the general health appreciably, we proceed with the irradiation immediately.

The course of irradiation usually lasts about three weeks, and during this time the patient must be under constant medical supervision. It is necessary to examine the blood repeatedly, because irradiation often produces anemia and leukopenia. These complications are met by transfusion and cessation of irradiation. In one of our cases, the white blood cell count dropped to 2,000 during the course of irradiation. We therefore discontinued the treatment immediately even though hardly half of the desired dosage had been utilized. In spite of this, however, the tumor had shrunk to approximately one-sixth its former size.

Gastro-intestinal symptoms may be present but are not disturbing. On the contrary, as the huge abdominal mass recedes, the appetite returns and it again becomes possible for the patient to eat with relish. When one sees how rapidly the mass is disintegrated and absorbed, one wonders what becomes of it and is surprised that the constitutional reaction is not more marked.

Severe hematuria may be a difficult problem. As a rule it diminishes after irradiation begins to take effect. In one of our patients, however, the urine remained blood-red until we irrigated the kidney with a solution of silver nitrate and enforced complete rest in bed.

Throughout the course of irradiation and after its conclusion, we make every effort to bring the patient to the peak of physical condition by diet, rest, tonics and sunshine. We have had no real difficulty in accomplishing this. We have postponed nephrectomy until we felt that the general condition made the operation safe.

The effect of this new operative regimen in the treatment of large renal tumors can be seen in the accompanying reports of cases. I hesitate to present a proposition which may be as important as this when it is supported by only limited experience. These patients, however, have all been observed in my own practice in the last three years and each has been thoroughly studied. In all but one instance, the roentgen therapy has been administered by Dr. Charles A. Waters. Those who are interested in the technic of these treatments are referred to his recent article on this subject.<sup>7a</sup>

*Transperitoneal Nephrectomy.*—The operative technic is also a matter of vital importance. Most urologists have been trained to carry out their operative procedures on the kidney through a lumbar incision. But for the purpose of removing tumors of the kidney the transperitoneal operation seems to be infinitely superior. The object of the operation is to remove the tumor intact with as much perirenal tissue as possible and with a minimum of handling and manipulation, for one knows how friable and vascular these tumors are and how frequently they invade the renal vein and its smaller intrarenal branches. Through a lumbar incision it is impossible to remove a renal tumor without extensive handling, and the last attachment to be controlled is the vital renal pedicle after the tumor has been exposed and delivered. This violates every object of the operation.

By the transperitoneal route, the whole process is reversed. Through a long rectus incision the peritoneal cavity is opened; the posterior layer of peritoneum lateral to the large intestine is cut, and the intestine is rolled medially. This imme-

---

7a. Waters, Charles A.; Lewis, Lloyd G., and Frontz, W. A.: Radiation Therapy of Renal Cortical Neoplasms. *South. M. J.* 27:290 (April) 1934.

diately brings one down to the capsule of the tumor. Further mobilization of the intestine and blunt dissection around the hilus of the kidney expose the renal pedicle which can be ligated and cut before one handles the tumor at all. Aberrant vessels can be seen easily because the exposure gives one a complete view of the whole flank and its contents. The tumor, thus deprived of its vascular connections, can then be removed without loss of blood or fear of disseminating metastases. Walker<sup>8</sup> advocated the principle of this operation in 1905, and Finney performed the operation with success and permanent cure twenty years ago. Our experience with both methods of approach compels us to agree with Finney that the extraperitoneal operation is the only method by which to remove a tumor of the kidney. It is a clean and scientific surgical procedure. In our last two patients, hemostasis was so complete and the wounds so clean that the abdomen was closed without drainage. The wounds healed by first intention, and the convalescence was normal.

#### REPORT OF CASES

To illustrate the proposition advanced in the foregoing portion of the article, I present a series of seven malignant renal tumors that have come under my care in the last three years. These are divided into three groups: first, large tumors in which nephrectomy was performed or attempted without preoperative irradiation; second, large tumors which were removed after preoperative irradiation, and third, small tumors that were removed without irradiation.

*Group I: Massive Tumors Not Receiving Preoperative Irradiation.*—This group comprises cases 1 and 2.

*CASE 1.—Diagnosis, a large hypernephroma of the left kidney, Grawitz type. Transperitoneal nephrectomy, October 1930. Death, three hours after operation.*

Mrs. K. W., aged 34, residing in Pennsylvania, had been under my care in 1927 for sterility, having been referred by Dr. Sydney R. Miller. A normal child was born in June 1930. She was delivered by a competent obstetrician, but apparently did not return to him for any postnatal observation. I examined her on Dec. 30, 1929, when she had been pregnant for about three months, and at that time one could not feel either kidney.

The case is particularly instructive because of the unusual rapidity with which the tumor must have developed after the birth of the child in June 1930, for when the baby was only 3 months old the patient returned to Baltimore wondering why her abdomen was getting larger instead of smaller. At that time casual inspection showed that she had a big tumor which filled three fourths of the abdomen. There had been no discomfort whatever, no hematuria and no loss in strength. The mass had grown so rapidly that I could hardly persuade myself that it was a solid tumor.

This case is another instance of the fearful operative toll in these big tumors. At operation in the Union Memorial Hospital the capsule of the mass was thin and intimately adherent to the peritoneum, the perirenal structures and the diaphragm. The capsule was broken, and the tissue of the tumor was implanted everywhere (fig. 1). There was no bleeding from the renal pedicle, but the

---

8. Walker, G.: Transperitoneal Ligation of the Renal Vessels, J. A. M. A. 45:1647 (Nov. 25) 1905.

enormous vessels that covered the tumor bled profusely. The tumor was removed through a long transperitoneal incision. The patient died of shock three hours later.

CASE 2.—*Hypernephroma of the right kidney, Grawitz type; diagnosed by biopsy, January 1932.*

Mrs. C. D., aged 51, had been discharged from a Baltimore hospital, where an exploratory laparotomy and biopsy revealed a huge hypernephroma. The husband had been told that nothing more could be done and that the outlook was hopeless. Through one of my friends, a house officer in the Johns Hopkins Hospital, he appealed to me for any suggestion. Without offering any hope whatever, I suggested that they might try high voltage roentgen therapy. The patient was therefore sent to the Hospital for Women, where the roentgenologist, Dr. Waters, took charge.

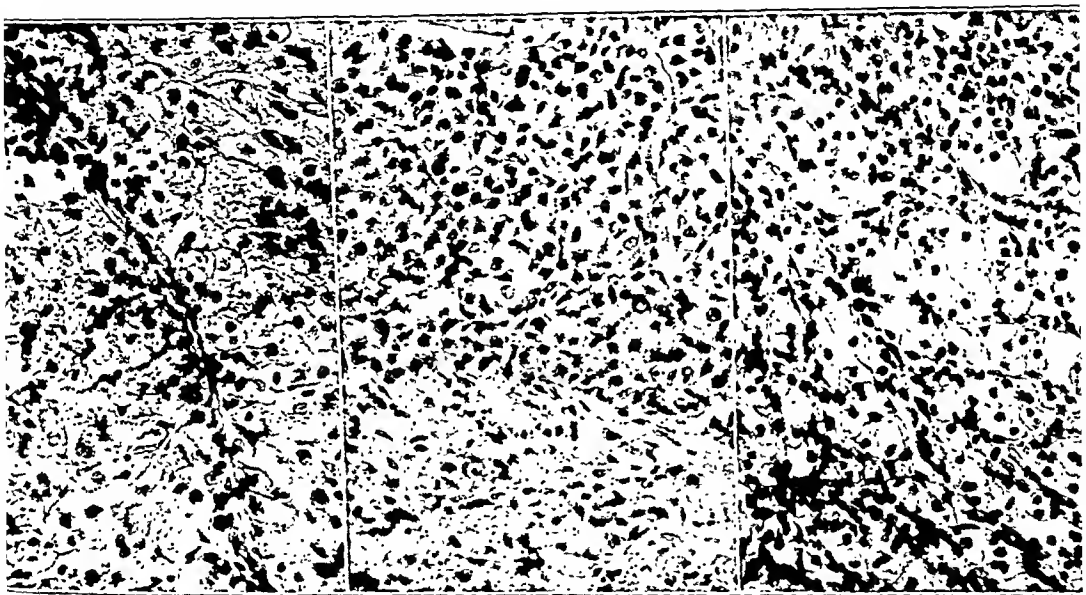


Fig. 1.—High power details of three hypernephromas of the Grawitz type from cases 6, 7 and 1, respectively. These tumors did not receive irradiation. This illustration should be compared with figure 5, which shows the same type of tumor after irradiation.

At the former operation, the tumor was found to fill the entire right half of the abdomen and to extend over into the left. The capsule of the tumor had been broken during the exploration of the mass and particles of the tumor scattered in the peritoneal cavity and abdominal wall. The right rectus incision had been closed after performance of a biopsy.

When the patient was admitted to the Hospital for Women six weeks later, her condition was precarious. The tumor extended from the seventh rib down to the pubis and across the midline of the abdomen (fig. 2). A recurrence of the growth soon developed in the abdominal incision, flank and iliac fossa. The temperature occasionally reached 104 F., the hemoglobin was 50 per cent, and the red blood cells numbered 3,000,000. Dr. Waters gave her a course of three trans-  
insions and high voltage therapy. He asked me to see her in March 1932. By

that time the tumor had receded to a point three fingerbreadths above the anterior superior spine. I advised further roentgen therapy and observation.

For the last two years, we have been watching this woman. She enjoys excellent health and has regained her strength completely; her blood is perfectly normal, and she has no discomfort except occasional attacks of abdominal pain which simulate partial intestinal obstruction. The mass has gradually decreased in size, so that now it extends only about three fingerbreadths below the costal margin in the lumbar fossa. There is, however, a persistent induration of the abdominal wall of the right flank down to the anterior superior spine and extending back to

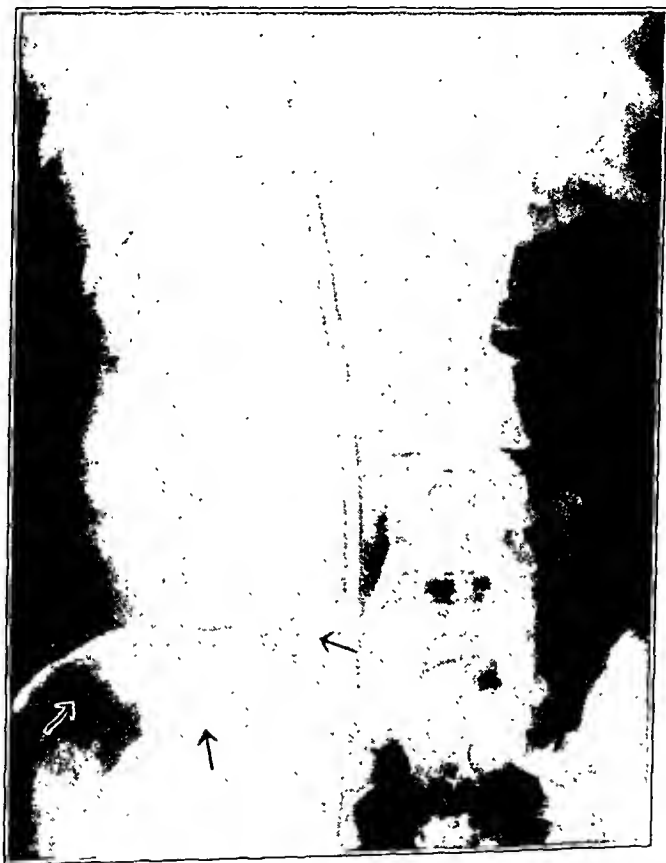


Fig. 2 (case 2).—Pyelogram showing a hypernephroma of the right side. The tumor was explored with biopsy in January 1932. The roentgenogram outlines the mass which filled the right half of the abdomen. Ninety per cent of this tumor disappeared after irradiation, and it would be easily operable if it were not for multiple implantations in the wound, peritoneum and lumbar fossa caused by premature exploration and biopsy. No metastases have occurred in almost three years, and the general health is good.

the erector spinae muscles. In the last month, I have thought that this induration has increased.

Through the last two years, we have been considering the advisability of removing this tumor, but have always decided that it would be futile. The diffuse induration in the flank and iliac fossa probably represents an active hyper-

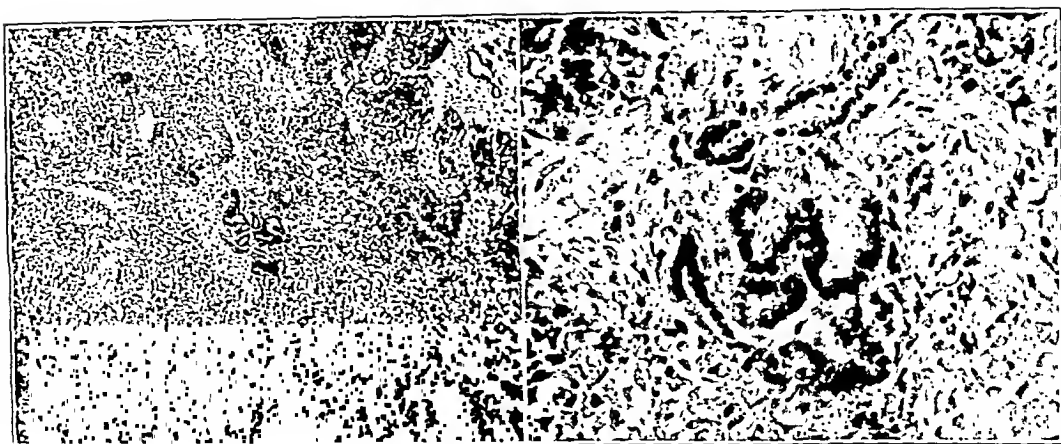


Fig. 3 (case 3).—Embryoma, Wilms' type, before irradiation. Note the solid masses of cells resembling those of a sarcoma, in which are scattered tubular masses. Compare this with figure 4.

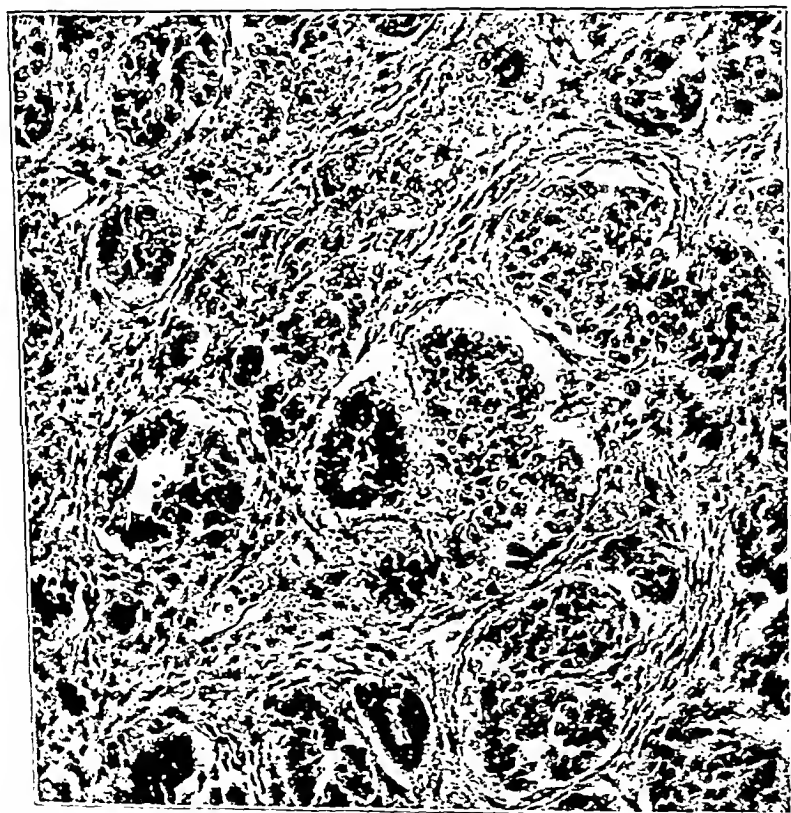


Fig. 4 (case 3).—Embryoma, Wilms' type, the same tumor as seen in figure 3, after irradiation and removal. Although the destructive effect of irradiation is not striking histologically, the decrease in the size of the tumor was perfectly satisfactory.



nephroma which would only be transplanted and stimulated by an operation. Furthermore, this patient has an extremely high blood pressure. For the time being, therefore, we have decided not to try to remove this growth, believing that she will live longer and more comfortably if it is controlled occasionally by roentgen therapy. If this tumor had not been explored and disseminated, it would have been easily operable.

*Group II: Massive Tumors Removed After Preoperative Irradiation.*—In this group are cases 3, 4 and 5.

*CASE 3.—Diagnosis, a large Wilms' tumor of the right kidney. Exploratory operation and biopsy, November 1933. Nephrectomy, January 1934.*

E. F., a child of 3 years, was seen at St. Joseph's Hospital in November 1933, ten days after nephrectomy had been attempted by another surgeon. He exposed the tumor through the lumbar incision without preoperative irradiation. The mass filled half of the abdomen. It was decided that the tumor could not be removed and, therefore, after a biopsy was made the wound was closed (fig. 3). When I was asked to see the child ten days later, it was evident that the only chance lay in reduction of the size of the tumor by irradiation. This was promptly begun by Dr. Howard E. Ashbury, the radiologist. Within one month this tumor was palpable only in the right renal fossa, and the general condition of the child was excellent. On Jan. 15, 1934, the tumor was removed by the surgeon in charge (fig. 4). The damage of the former biopsy, however, was evident in the dense adhesions. The tumor was again ruptured during its removal and it had to be cut away from the old wound in the lumbar fossa. In this case I feel that the chance of cure has been definitely lessened by the premature biopsy.

*CASE 4.—Diagnosis, hypernephroma of the right suprarenal gland, Grawitz type; normal kidney. Right nephrectomy and removal of the right suprarenal gland and tumor, Oct. 12, 1933.*

When C. S., a Negro girl, 2½ years old, was admitted to the Provident Hospital in August 1933, she had evidently only a short time to live. She was emaciated, and her temperature was 105 F. The abdomen was distended by a huge mass which crossed the midline and filled every quadrant except the left iliac fossa and the extreme left side. The hemoglobin was around 50 per cent and the red blood cell count below 3,000,000. The mother had noticed the tumor three months before, but did not bring the patient to the dispensary of the hospital for the colored until the child became emaciated. There had been no hematuria. There was sexual precocity; the pubic hairs were well developed.

It was obvious that the child was in no condition for either operation or irradiation. Repeated small transfusions were therefore given, and eventually a course of intense, but carefully measured roentgen therapy was carried out. The effect was miraculous. Within three weeks, nine tenths of the tumor had gone (figs. 5 and 6), and one could just feel it below the costal margin in the right lumbar region. Irradiation was continued for about a month.

The medical care was conducted by Dr. Lawson Wilkins, the consultant in pediatrics at the Provident Hospital. By Oct. 12, 1933, or in about seven weeks from the time of admission, we thought that the condition warranted the risk of the operation. The hemoglobin had reached 70 per cent, the mass could not be felt at all and the child was apparently in perfect health.

The operation was easily performed, although we were surprised at what we found. We used a long right rectus incision which gave perfect exposure to the whole right flank. The right kidney was completely normal, but behind and above

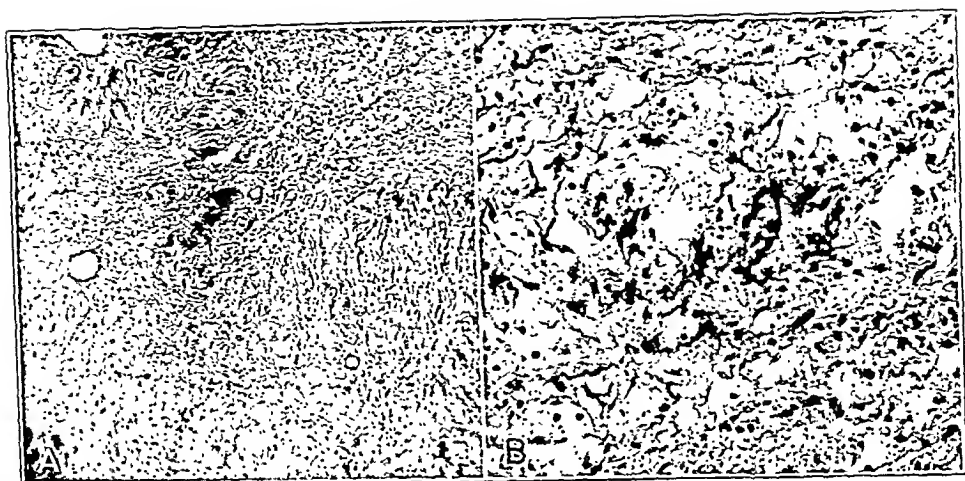


Fig. 5 (case 4).—Hypernephroma, Grawitz type, after irradiation. Notice the areas of hyalinization, pyknosis, deposit of pigment, destruction of the architecture of the tumor and cellular degeneration. (Photomicrograph on the left,  $\times 100$ ; that on the right,  $\times 300$ .)



Fig. 6 (case 4).—Hypernephroma, Grawitz type, of the right suprarenal gland in a girl of  $2\frac{1}{2}$  years. The rapid decrease in size of the tumor following irradiation is shown. Thirteen days after irradiation was begun, the tumor could be just felt under the ribs. Figure 5 shows the histologic appearance of this tumor.

it lay a mass of almost exactly the same size and shape as the kidney itself. It was adherent to the posterior surface of the kidney but distinctly separate from it. The mass was attached by a broad pedicle high up and behind the renal pedicle. The tumor was rather firm, enclosed in a dense fibrous capsule and not particularly adherent to the diaphragm or the walls of the lumbar fossa.

The vessels of the kidney were clamped and ligated before we had mobilized the kidney at all, or before we were aware that the tumor was connected with the suprarenal gland. As we mobilized the kidney we saw that the mass was behind it. We removed the kidney first, thus obtaining an excellent view of the suprarenal gland and the tumor. After liberating the tumor the pedicle was clamped and the entire mass removed (fig. 7). There was no bleeding or shock.

The convalescence was uneventful. It is, of course, impossible to predict the future for this child. Before operation, with the tumor she weighed 27 pounds (12.2 Kg.); one month later she weighed 32 pounds (14.5 Kg.). She appears to

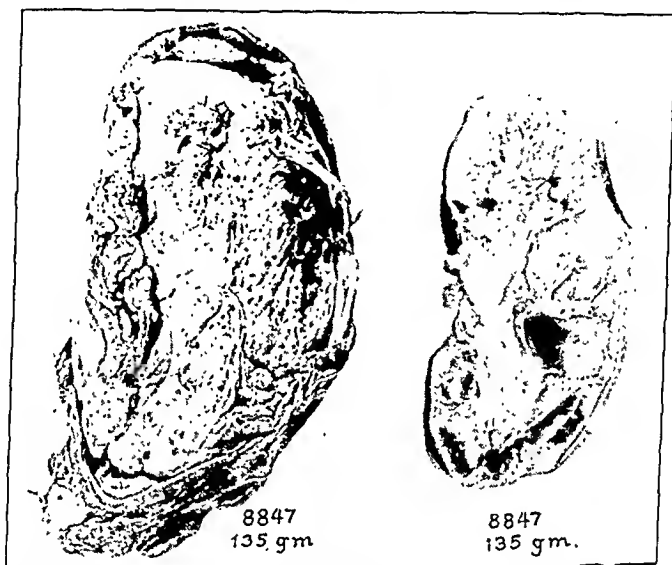


Fig. 7 (case 4).—Hypernephroma of the right suprarenal gland and the normal right kidney removed with it. Each weighed 135 Gm.

be perfectly well. We are arranging to have her return for observation every month until we are satisfied that the danger of recurrence is past.

*CASE 5.—Diagnosis, a large Wilms' tumor on the left side.*

Miss B. M., aged 16, first noticed blood in the urine during the summer, 1932, but was not referred for diagnostic study until August 1933. By that time, the patient had become emaciated and had an abdominal mass which looked like an advanced pregnancy. When I saw her in August 1933, she was so weak that she could hardly get out of bed and was very thin and pale. One could see the prominent mass which extended from the left flank across the midline to the region of the gallbladder and thence down below the umbilicus toward the pelvis (fig. 8). A blood count showed: red cells, 3,200,000; white cells, 2,200, and hemoglobin, 45 per cent. The urine was red with blood. The patient was immediately sent into the Church Home where a transfusion was given. By the usual urologic means, the diagnosis of renal tumor was made; no metastases were evident radiologically or clinically.

We experienced considerable difficulty in restoring this girl to a satisfactory physical state because of the profuse hematuria and the leukopenia. The hematuria persisted even after the tumor had been irradiated, and this wiped out the benefit of repeated transfusions. Finally, we controlled the bleeding by renal lavage with a solution of silver nitrate and by complete rest.

The leukopenia was even more troublesome. It was present before the patient received any irradiation (2,200 white blood cells) and became more marked afterward. At no time, however, did differential stains reveal any organic disease of the blood-forming organs. Six weeks after irradiation had been stopped, the white

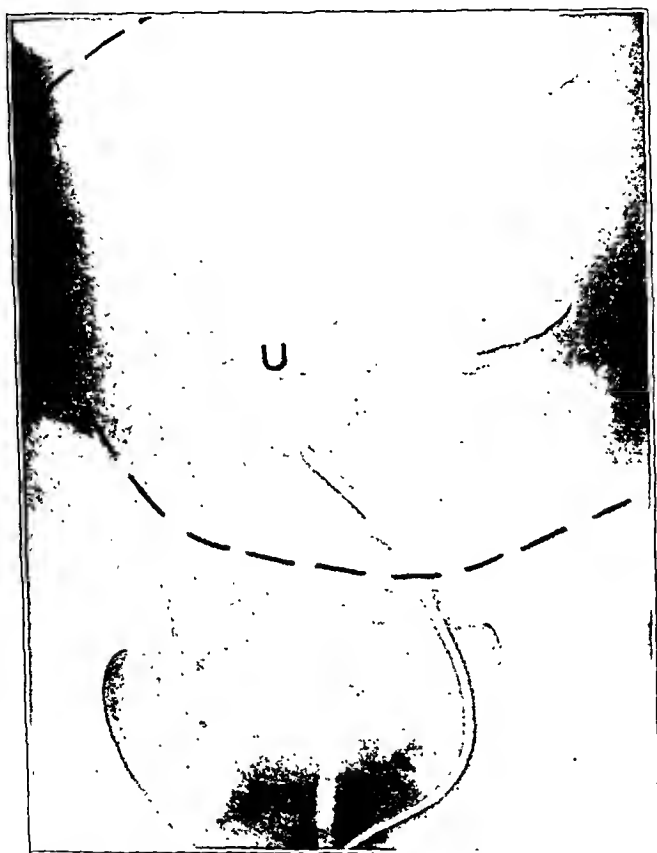


Fig. 8 (case 5).—Retrograde pyelogram of an embryoma of the left kidney before irradiation. The mass fills most of the upper and left parts of the abdomen.

blood cells numbered 5,600, the differential count was normal and the hemoglobin was 76 per cent.

Because of the leukopenia, however, we stopped irradiation before the desired dose had been given. For this reason, perhaps, the tumor did not shrink as completely as it might have done otherwise. Nevertheless, as shown in figure 9, the entire abdominal mass disappeared, leaving only the mass in the flank and under the diaphragm.

The improvement in the general condition was also remarkable. During the first month after irradiation, the girl gained 16 pounds (7.3 Kg.) and looked and

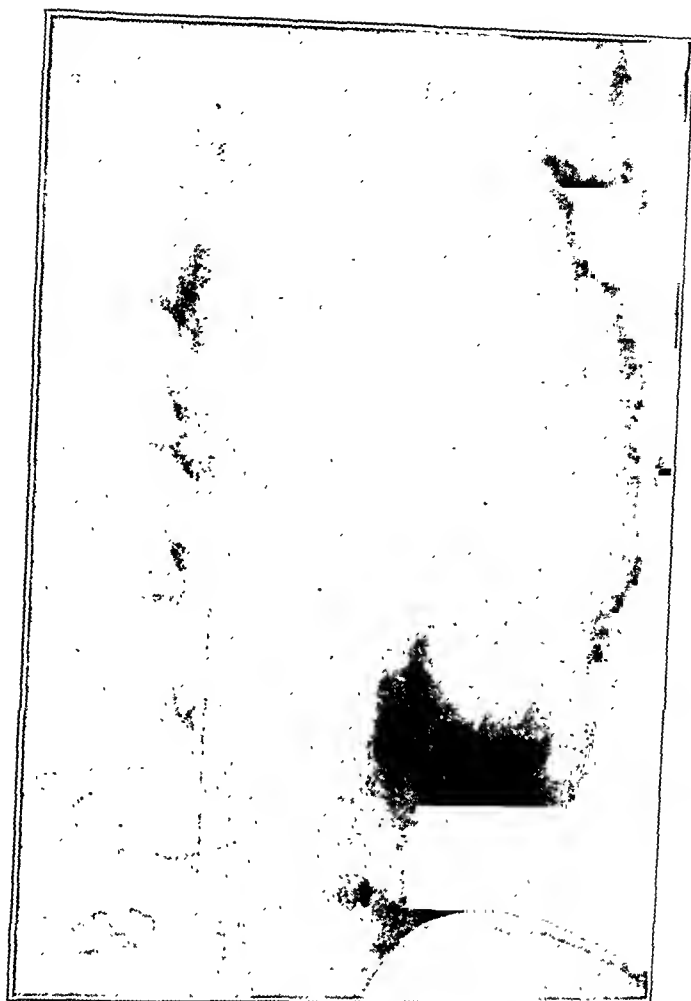


Fig. 9 (case 5).—Intravenous pyelogram taken of the tumor after irradiation. The abdominal mass has entirely disappeared; there is still a mass under the diaphragm as large as a child's head. The pelvis of the kidney before irradiation was opposite the fourth and fifth lumbar vertebrae (compare figure 8); after irradiation, it lies opposite the second and third lumbar vertebrae.

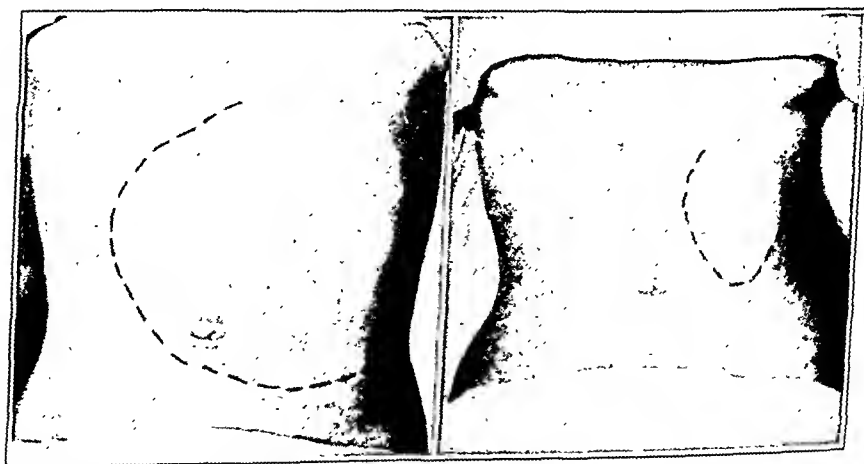


Fig. 10 (case 5).—Embryoma of the Wilms' type in the left kidney of a girl of 16. The remarkable decrease in the size of the tumor in eighteen days was accomplished with half the usual roentgen dosage. See the text, figures 8 and 9, for pyelograms taken before and after irradiation, and figure 11 for histologic characteristics.

felt perfectly well. We were compelled to defer operation, however, beyond the optimum time because of the reluctance of the parents. During this month of procrastination, the tumor definitely increased in size. The patient herself settled the question of operation when she had a recurrence of severe hematuria seven weeks after the course of irradiation had ended.

A left transperitoneal nephrectomy was performed at the Church Home on Nov. 27, 1933. This case, like the preceding one, stands out in sharp contrast to those in which irradiation was not given. Although we had to remove a tumor as large as a man's head, the long left rectus incision gave us excellent exposure to the tumor and the renal pedicle, for the abdominal mass had disappeared entirely. The pedicle was ligated before the tumor was mobilized. There were several large aberrant vessels which were seen clearly and ligated. The suprarenal gland was almost enveloped by the tumor, and it was removed with the tumor in one mass. The patient was on the operating table about an hour and fifteen minutes. The convalescence was uneventful.

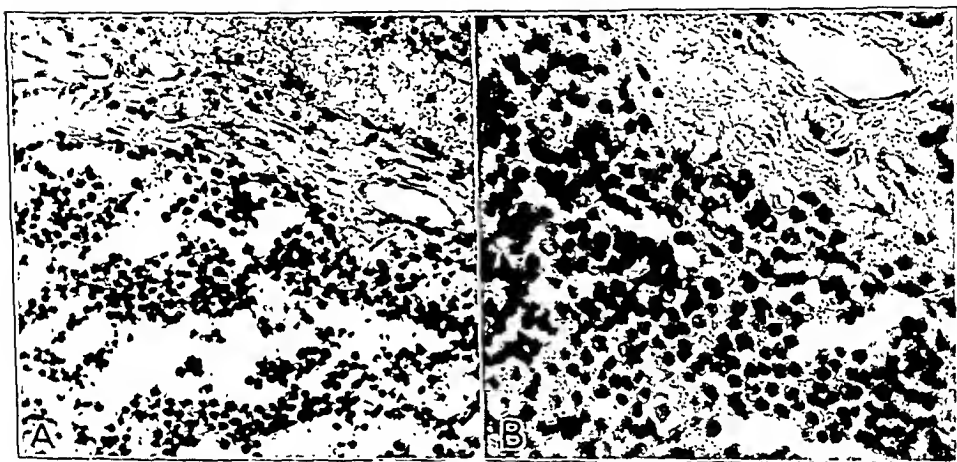


Fig. 11 (case 5).—Embryoma, probably of the Wilms' type, after irradiation. Here again the destructive action is evident although only half the desired dose of irradiation could be utilized. (Photomicrograph on the left,  $\times 55$ ; that on the right,  $\times 300$ .)

*Group III: Small Tumors Removed Without Irradiation.*—These cases are presented for three reasons: to show the ease with which a small hypernephroma can be removed; to commend the example of the general practitioners who recognize the seriousness of hematuria, and to contrast the pathologic structure of tumors before and after irradiation.

*CASE 6.—Diagnosis, hypernephroma of the right kidney, Grawitz type. Extra-peritoneal lumbar nephrectomy, Jan. 9, 1932.*

Mrs. M. R., aged 52, entered the Union Memorial Hospital with the complaint of a painless hematuria, which had been noticeable for only three days. Six months previously, the urine had been examined by her family physician, Dr. James Akehurst, and found to be normal. It is interesting that three years previously I performed a panhysterectomy on this woman's sister for carcinoma of the body

of the uterus, and so far there has been no recurrence. The family doctor sent her for a cystoscopic study as soon as he discovered the hematuria.

By the usual cystoscopic studies, we made a diagnosis of hypernephroma, and on Jan. 9, 1932, we removed the right kidney. The tumor was small, not more than 5 cm. in diameter (fig. 1). The operation was easily performed. The convalescence was uneventful and the patient has shown no evidence of recurrence.

*CASE 7.—Diagnosis, hypernephroma of the left kidney, Grawitz type. Left lumbar nephrectomy, March 3, 1932, Sinai Hospital.*

Mrs. M. R., aged 48, like the patient in case 6, had had hematuria for only a short time, four days. It had been accompanied by a dull ache in the region of the left ureter and kidney. There were no other symptoms. Again the family physician, Dr. Samuel Whitehouse, demanded immediate investigation as soon as the hematuria was reported to him.

After the usual cystoscopic procedures (bilateral pyelograms, functional tests, cultures and urinalysis) the diagnosis of a hypernephroma of the left side was made. In this case, however, the diagnosis was made in spite of two sets of pyelograms which showed no sure sign of tumor. Since the patient had unilateral, unexplainable hematuria and since I could just feel the lower pole of the left kidney, I decided that we were dealing with an enlarged left kidney and probably an early hypernephroma (fig. 1). On March 3, 1932, I removed the tumor and thus far there is no evidence of recurrence.

#### SUMMARY

In summarizing my own experience with the surgical removal of renal tumors in the last three years, I cannot escape the conclusion that life has been prolonged and probably saved by the use of preoperative irradiation. The histories of five patients with massive malignant tumors have been presented. Three of these patients were operated on by different surgeons in Baltimore without preoperative irradiation. All three operations were failures; one patient died of shock three hours after nephrectomy and the other two had only biopsies. I have presented a group of four cases of massive tumors that were treated by high voltage roentgen therapy for the purpose of decreasing their size so that they might be removed in safety. Two of these tumors were operated on without any complication or difficulty whatever. Both of these were in children, among whom the mortality has always been very great. The third tumor, which had previously been explored and declared inoperable, was later irradiated successfully and removed, but the harm done by the premature biopsy was probably beyond repair. The fourth large tumor was also explored prematurely, but has since been largely destroyed by irradiation. I fear, however, that in this case also, the dissemination of the tumor by the biopsy has made the situation hopeless.

The last two cases of small hypernephromas were included merely to reinforce the statement that the most serious single handicap in the removal of renal tumors is their great size. Small tumors usually offer little operative difficulty.

## CONCLUSIONS

1. A review of the literature shows that up to the present the results in the surgical treatment of renal tumors have been highly unsatisfactory. From 5 to 10 per cent of the patients are refused operation because of the evident metastasis or the apparent impossibility of removing the local growth; from 12 to 26 per cent have only exploratory operations; from 15 to 30 per cent die of surgical shock after nephrectomy, and of the remainder, less than 10 per cent are permanently cured.

2. The greatest single cause of this high mortality is the enormous size of these tumors, which prevents complete surgical removal, causes a high operative death rate and favors local recurrence and metastasis.

3. In my experience, preoperative irradiation of both Wilms' and Grawitz' tumors causes a remarkable decrease in their size and makes them easily operable.

4. Preoperative irradiation also causes definite cellular changes in the malignant tissue, such as hyalinization, pyknosis, fragmentation and destruction of the architecture of the tumor.

5. Irradiation, however, will not destroy malignant tumors entirely. After having been intensively irradiated, tumors which I have removed have uniformly shown living malignant tissue; those which I have not removed have resumed active growth. Roentgen therapy is only a means of preparation to make the tumor operable, or a palliative measure to hold in check a tumor which cannot be removed.

6. The experience of my colleagues and myself with preoperative irradiation of massive renal tumors has caused us to institute an entirely new regimen in preparing these patients for operation.

7. I cannot urge too strongly the advantages of the transperitoneal approach as the most logical, clean and surest way to remove tumors of the kidney.

Dr. Arnold R. Rich, associate professor of pathology in the Johns Hopkins Medical School, studied the sections from some of these tumors, particularly those which had been irradiated.

1201 North Calvert Street.



# HEMORRHAGIC VILLOUS SYNOVITIS OF THE KNEE JOINT DUE TO XANTHOMA

## REPORT OF A CASE

DAVID H. KLING, M.D.

LOS ANGELES

AND

DAVID SASHIN, M.D.

NEW YORK

The occurrence of hemorrhagic effusion into the knee joint due to xanthoma is very uncommon. In a review of the literature only five cases have been reported. In view of the extreme rarity of this condition we are reporting the following case.

## REPORT OF CASE

*History.*—W. M., aged 23, white, American born, a garage hand, was admitted to the service of Dr. Harry Finkelstein, Hospital for Joint Diseases, New York, on March 7, 1932, suffering from a painful swelling of the left knee, which had increased in size during the past two years. There was no history of trauma.

He had had occasional pain in the shoulders since the age of 13. He had gonorrhea in 1930, for which he received treatment and was discharged as cured. Appendectomy was performed in 1920. His parents and one brother and sister were in good health. There was no family history of arthritis, tuberculosis or hemophilia.

*Physical and Laboratory Examinations.*—The patient was well developed and well nourished, but somewhat pale. The physical findings were insignificant except for the local condition. The left knee joint was enlarged with some increase of local temperature. There was ballottement of the patella, with definite fluctuation in the joint. The range of motion was decreased. The roentgenograms, taken outside of the hospital two weeks before admission, showed nothing abnormal.

Aspiration from the left knee joint yielded 50 cc. of a frankly bloody fluid of a thick consistency.

Tests for the Wassermann and gonorrheal complement fixations in the fluid and blood and the inoculation of a guinea-pig gave negative results.

Seven days later, March 14, the fluid had reaccumulated and by a second aspiration a hemorrhagic fluid was again recovered. The knee was strapped. Four days later there was a recurrence of the fluid in the knee and a third aspiration of hemorrhagic fluid was performed. The knee was again strapped and rest in bed was advised. The icterus index of the fluid was 58.8. One week later (March 25) the fluid had reaccumulated, and a fourth aspiration yielded 60 cc. of hemorrhagic fluid. After the aspiration a freely movable body, the size of a cherry, was felt over the head of the fibula. The icteric index in the joint fluid was 50.

---

From the service of Dr. H. Finkelstein, Hospital for Joint Diseases, New York.

Urinalysis gave negative results.

Examination of the blood showed the bleeding time to be two minutes; the coagulation time, one and a half minutes.

A complete blood count gave the following results: hemoglobin, 85 per cent; red blood cells, 4,540,000; white blood cells, 12,200; neutrophils, 59 per cent; eosinophils, 2 per cent; lymphocytes, 27 per cent, and monocytes, 2 per cent.

Tests for the fragility of the red blood cells showed initial hemolysis in a 0.42 per cent saline solution, complete hemolysis in a 0.38 per cent solution.

The roentgenograms of the left knee showed nothing abnormal.

The diagnosis of a villous hemorrhagic synovitis with a possible polyp was made, and the patient was admitted to the hospital for operation. Although the fluid had reaccumulated, the knee was free from pain and motion was normal. The circumference of the left knee was 14 inches (35.5 cm.); that of the right, 13½ inches (34.3 cm.).



Fig. 1.—Portions of the synovial membrane showing the synovia thickened and diffusely studded with villi. The dark areas seen in the section were a dark reddish brown.

An operation was performed on April 7.

*Operative Procedure.*—An arthroscopy and synovectomy were performed. The arthroscopy by Dr. Burmann showed an excessive amount of bleeding when the nick in the skin was made previous to introducing the instrument. Bloody fluid escaped from the trocar and could be partially cleared only by repeated washing. The joint appeared to be filled with dark brown fibrin. The infrapatellar pad of fat protruded into the joint and the internal condyle was brownish.

A synovectomy was then performed by one of us (Dr. Sashin). A parapatellar incision was made extending from the tibial tuberosity to the apex of the pouch of the quadriceps. The knee joint was found to be filled with a fibrinous clot and adhesions. The synovia was dark red or brownish and thickened. Masses of hemorrhagic polypoid villi were found in the quadriceps pouch. The menisci, crucial ligaments and articular surfaces were found intact. All of

the accessible synovia was removed (fig.1). One large vessel was secured by a deep suture. The wound was closed in layers with chromic gut for the deeper tissues and silk for the skin. A compression dressing was applied with a molded posterior plaster splint.

*Microscopic Examination* (Dr. Jaffe).—Sections showed a hypertrophied synovia with the formation of villi. The hypertrophied folds contained large numbers of newly formed blood vessels with considerable blood pigment and some giant cells (figs. 2 and 3). As yet there was no great number of phagocytes. The vascular appearance did not indicate that the lesion was primarily an angioma. The primary cause of the lesion could not be demonstrated in the slide. It was related to the polymorphocellular, xanthoma-like or angioma-like

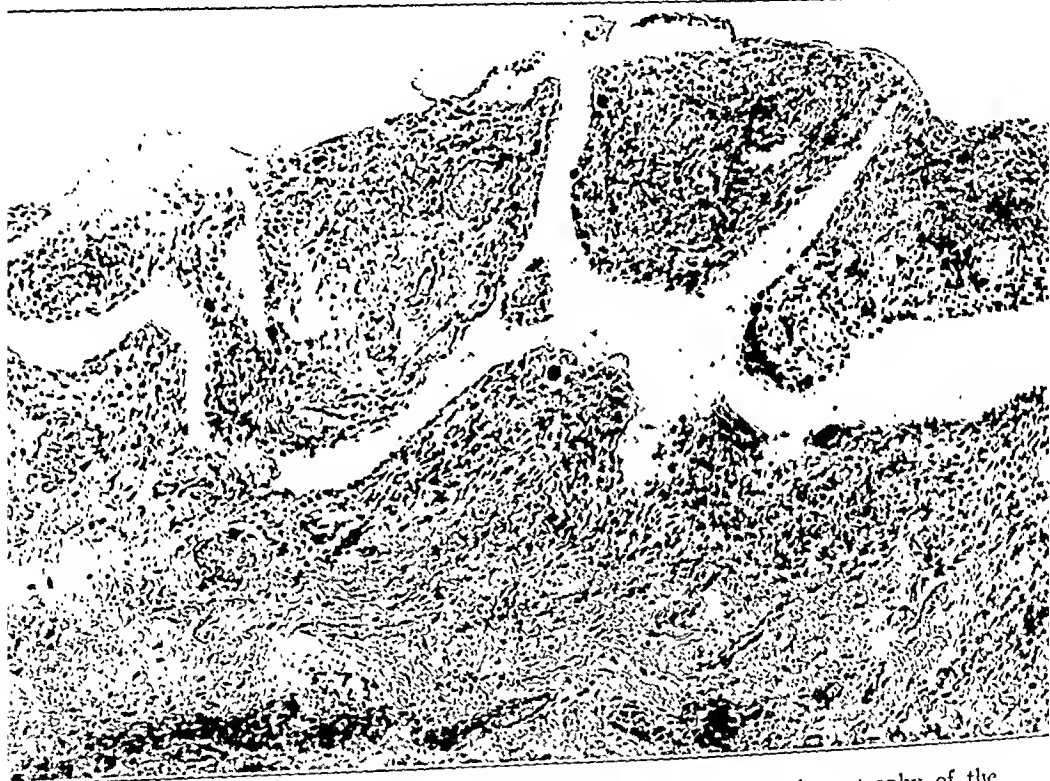


Fig. 2.—Low power magnification of a section showing a hypertrophy of the synovial membrane with the formation of numerous villi.

lesion encountered in the joints, especially the knee joints, and on tendon sheaths, the etiology of which is unknown. The lesion is not a tumor though it is often loosely described as such. As judged from the sections this seemed to be an earlier phase of the type of lesion that may grow to large proportions in the knee joint, complete removal of which produces a cure.

Smears from the synovial membrane showed occasional pus cells and no bacteria. Cultures from the membrane were sterile after four days.

*Postoperative Course.*—In the evening after operation the temperature rose to 101.8 F. The patient suffered pain in the knee joint and had to be given sedatives. The temperature persisted between 99 and 101.3 F. for about ten days.

and returned gradually to normal. On April 12 the posterior splint was removed, and active and passive motion was begun. Motion improved, with no recurrence of fluid.

The patient was discharged on April 23 with extension of the knee to an angle of 180 degrees and flexion up to an angle of 150 degrees. He subsequently received diathermy, massage and exercises for the left knee. Flexion improved to 135 degrees and the treatment was discontinued on June 8.

A check-up examination on August 3 showed the knee to be in excellent condition. The angle of greatest extension was 180 degrees and that of greatest flexion, 125 degrees. There was no pain, tenderness or fluctuation. The patient

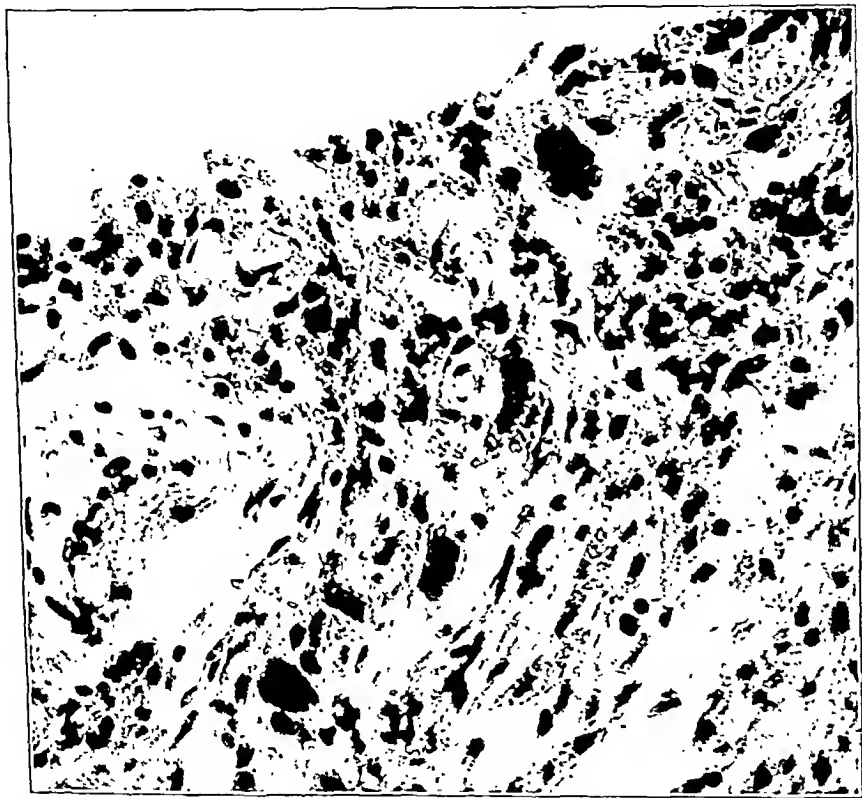


Fig. 3.—High power magnification of a section of synovial membrane showing giant cells, numerous blood vessels and a large increase of synovial cells.

was advised to return in about six months. Reexamination on December 23 showed full range of extension and flexion up to an angle of 70 degrees. The knee was in excellent condition. At this time the cholesterol content of the blood was 288 mg. per hundred cubic centimeters: on March 6, 1933, 240 mg., and on April 15, 238 mg.

#### COMMENT

The characteristics of this case are as follows: A diffuse, villous, hemorrhagic hypertrophy of the synovia, especially in the suprapatellar pouch, had reached tumor-like dimensions. The dark red and brown color showed the presence of numerous vessels which were easily vulner-

able and had produced old and recent hemorrhages. Yellowish patches, characteristic of xanthoma, were present. Studied microscopically, the villi showed numerous rows of cells of the type seen in the synovial lining and a stroma of fibroblasts, numerous large and small vessels and giant cells. The last-mentioned cells had the characteristics of giant cells of the foreign body type rather than of those of the tumor type. The vesicular nuclei were deeply stained and showed a margin of protoplasm. Lesions of this kind are classified either as tumors or as granulomas. They occur rarely. Only about fifty such tumors have been reported to date. This number includes spindle and round cell sarcomas of the capsule or bone with infiltration of the synovial membrane, and cavernous hemangiomas which also have broken into the joints from the surrounding tissues. The largest single group is made up of inter-articular giant cell tumors, also called benign xanthomatous sarcomas of the knee joint.

#### REVIEW OF LITERATURE

Eric Sonntag<sup>1</sup> has collected twenty cases from the literature. Of these sixteen cases presented localized growths in the synovial membrane of the knee joint. In only four cases were there diffuse lesions comparable to our own case. Among the latter group the first case of Lejars and Rubens-Duval<sup>2</sup> showed different characteristics. The tissue did not contain giant cells, but was made up in some places of spindle cells, and in others of glandlike arrangements of endothelial cells containing mucin. The case of Dowd,<sup>3</sup> published in 1912, should be excluded, as the tissue contained only a moderate number of blood vessels and the fluid in the joint was clear; also the giant cells showed mitotic figures not encountered in the xanthoma. No xanthoma cells were found in this case. The case of Harbitz<sup>4</sup> should not be included in this group as it was that of a diffuse endothelioma, partly calcified and also infiltrating the bone. In this group, therefore, there remains only one case, that of Hartman,<sup>5</sup> described in 1922. The patient was a man of 20, who for four years had complained of pain in the knees. Frequent aspirations revealed bloody fluid. At operation blood was

1. Sonntag, E.: Ueber intraartikuläre Xanthome des Knies, *Deutsche Ztschr. f. Chir.* **223**:346, 1930.

2. Lejars and Rubens-Duval: Les sarcomes primitifs des synoviales articulaires, *Rev. de chir., Paris* **41**:751, 1910.

3. Dowd, C. N.: Villous Arthritis of the Knee, *Ann. Surg.* **56**:363, 1912.

4. Harbitz, F.: Tumors with Xanthoma Tissue, *Norsk mag. f. lægevidensk.* **86**:321, 1925.

5. Hartman, F. W.: Synovial Membrane Tumors of Joints, *Surg., Gynec. & Obst.* **34**:161, 1922.

found in the synovial cavity. The synovial membrane was very thick and studded with villi of reddish brown or fawn; the cartilage in the crucial ligaments was also involved. The microscopic sections showed the capsule to be thickened and to contain brownish pigments, large and small villi and an abundance of large and small vessels. The stroma was made up of the following types of cells: monocytes, sometimes with pigments; oval cells, either single or in collections, with small blue nuclei and clear granular protoplasm; occasional giant cells, and, finally, foamy cells which contained double refractive lipoid material from which crystals of cholesterol could be obtained.

A second case of diffuse xanthoma was reported in 1927 by Herxheimer<sup>6</sup> in a woman 30 years of age. Histologically, spindle cells, giant cells and xanthoma cells were found. A third case was reported by Frangenheim<sup>7</sup> in 1928, that of a man of 50 who had suffered a dislocation of the left patella in 1904 and had had intermittent effusions. He was free from disability until 1924, when he noticed a growth in the popliteal fossa. The operation showed polygonal cells, giant cells, hemorrhages and pigment. He had a recurrence after six years, with pain and effusion. At operation the synovial membrane was found to be hemorrhagic and villous, and contained numerous blood vessels and capillaries, giant cells and "osteoid stroma."

In addition two cases described as hemorrhagic villous arthritis by Koch<sup>8</sup> and Mandl<sup>9</sup> belong to this group. Koch's case was that of a girl of 22 in whom pain and swelling of the right knee joint developed in 1924. At operation the synovia was found to be much thickened with large clots of blood in the cavity and thrombosis of the vessels. Histologic examination showed a very vascular tissue with numerous fibroblasts and blood pigment. Three years later there was a recurrence and the patient again submitted to operation. The synovia was found to be hemorrhagic and villous. On microscopic examination, numerous vessels, infiltration of pigment and giant cells of the foreign body type were found. Mandl's case was that of a man of 30, who had suffered an indefinite injury, followed by development of pain and swelling of the knee with occasional locking. Aspiration of fluid from the knee joint was performed fifty times. He received baths, bandaging, and

---

6. Herxheimer, G.: Ueber Xanthome und Xanthelasma, *Arch. per le sc. med.* **50**:201, 1927.

7. Frangenheim, P.: Das gutartige xanthomatöse Riesenzellensarkom der Gelenkkapsel, *Arch. f. klin. Chir.* **157**:738, 1929.

8. Koch, H.: Chronische hämorrhagische Arthritis des Kniegelenks, *Zentralbl. f. Chir.* **54**:2892, 1927.

9. Mandl, F.: Ueber die operative Behandlung chronischer nichtspezifischer Erkrankungen des Kniegelenks, *Arch. f. klin. Chir.* **151**:302, 1928.

injections into the joint. An operation was done in October 1926. On the medial aspect of the synovial membrane, brownish-red villi were observed, which histologically contained several rows of synovial lining cells, numerous vessels, lymphocytes and plasma cells with much blood pigment. A partial synovectomy was done, but there was a recurrence of symptoms and a second operation was performed a year later. The whole synovial membrane was then found to be covered by brownish-red villi which contained numerous blood vessels, several rows of synovial cells, a large amount of blood pigment and islands of light cells with double refractive protoplasm which gave a positive stain for fat, characteristic for xanthoma.

#### PATHOGENESIS

The pathogenesis of these conditions is still controversial. The first observers considered them to be tumors of sarcomatous character. In 1898 Dor,<sup>10</sup> who discovered the xanthoma cells, advanced the theory of an inflammatory and traumatic origin for this growth, and was supported by Fleissig,<sup>11</sup> Wustmann<sup>12</sup> and others. Seyler<sup>13</sup> held an intermediate view, and of ten cases he regarded three as granulomas. The arguments for the blastoma theory were well summarized by von Albertini<sup>14</sup> and for an inflammatory origin by Sonntag. Von Albertini regarded the giant cell tumors of the periosteum, bone, tendons and joints as of identical structure. They originate from an embryonal mesenchyme which has not undergone complete differentiation and is, therefore, apt to develop giant cells. The numerous vessels present in these growths are explained by the canalization of loose mesenchymal tissue. The second characteristic element is the xanthoma cell which is found only in giant cell tumors of the tendons and joints, and not in epulides or giant cell tumors of the bone. This can be explained by a disposition of the skin, tendons and joints to precipitation of lipoids. In the multiple xanthomas of the skin this occurs on the basis of a hypercholesteremia, analogous to the formation of tophi in gout. In the solitary giant cell tumors of the joints and tendons, hypercholesteremia

10. Dor, L.: Relations des tumeurs à myeloplaxes et des xanthomes, *Compt. rend. Congr. franç. de Chir.*, 1898, p. 553.

11. Fleissig, J.: Xanthomatöse Geschwülste, *Deutsche Ztschr. f. Chir.* **192**:380, 1925.

12. Wustmann, O.: Xanthomatous Giant Cell Tumors, *Deutsche Ztschr. f. Chir.* **192**:381, 1925.

13. Seyler: Ueber xanthomatische Granulome, *Virchows Arch. f. path. Anat.* **239**:20, 1922.

14. von Albertini, A.: Spezielle Pathologie der Sehnen, Sehnenscheiden und Schleimbeutel, in Henke, F., and Lubarch, O.: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1929, vol. 9, p. 556.

was found only in a part of the cases. Kirch<sup>15</sup> collected eight cases in which the cholesterol content of the patients varied between 481 and 173 mg. per hundred cubic centimeters of blood. The normal cholesterol content of the blood varies between 140 and 160 mg. In the cases in which the cholesterol content of the patient's blood was normal, the presence of xanthoma cells was explained by the precipitation of lipoids, especially cholesterol, from a hematoma, or as due to stagnation of circulation and deficiency of absorption. Von Albertini advanced the following arguments against the conception of these growths as granulomas: Only exceptionally are inflammatory granulations found. Bacteria have never been demonstrated in these growths. The giant cells have no relation to the vessels and, therefore, do not originate from the endothelium of vessels, as proposed by Lubarsch.<sup>16</sup> They also are not giant cells of the foreign body type attracted by the precipitation of cholesterol, as the majority do not contain cholesterol in the plasma, and do not accumulate in the vicinity of the precipitation of the lipoids. He, however, admitted that besides genuine blastomatous giant cells there are present giant cells of the foreign body type, chiefly around the blood pigment. He did not regard the experiments on animals as conclusive. Anitschikow<sup>17</sup> and others have produced xanthomatous growths in tendons of animals fed with a diet rich in cholesterol, or animals which had been given intravenous injections of cholesterol and subsequently traumatized. Von Albertini regarded these lesions only as lipophagic foreign body cell granulomas without the characteristics of true giant cell tumors.

Eric Sonntag advanced the following arguments for the theory of the inflammatory origin of the xanthomatous tumors: The stroma of the growths is a typical granulation tissue consisting of fibroblasts, lymphocytes, polymorphonuclear leukocytes, partly sclerotic scar tissue, blood pigment and crystals of cholesterol surrounded by giant cells. The giant cells have vesicular, only faintly stained nuclei and a definite protoplasmic border. Blastoma giant cells have oval, heavily stained nuclei, and they do not show protoplasmic borders. Both authors agreed, however, that the xanthomatous cells in these growths are only secondary, and are produced in response either to a hypercholesteremia or to a local disturbance of lipid metabolism.

---

15. Kirch, E.: Ueber cystische xanthomatöse Geschwülste und die Genese des xanthomatösen Geschwülste im allgemeinen, Beitr. z. path. Anat. u. z. allg. Path. 70:75, 1922.

16. Lubarsch, O.: Generalisierte Xanthomatöse beim Diabetes, Deutsche med. Wchnschr. 18:484, 1918.

17. Anitschikow, N.: Ueber experimentell erzeugte Ablagerungen von Cholesterinestern und Anhäufungen von Xanthomzellen im subkutanen Bindegewebe des Kaninchens, München. med. Wchnschr. 40:2555, 1913.



## DIAGNOSIS AND TREATMENT

The general symptoms of this condition are not characteristic. The patient complains of a swelling of the knee joint, pain, a limp in walking and sometimes of locking of the knee joint. The onset is insidious. Only part of the patients give a history of a definite injury. On examination, swelling, limitation of motion and fluctuation are found. In localized tumors a definite mass, more or less freely movable, can be palpated. The symptoms are therefore not different from those in an internal derangement or inflammatory condition. Most of the patients therefore come to operation with a diagnosis of loose cartilage or tuberculosis of the knee joint.

The diagnosis, however, can be definitely established by an aspiration and thorough examination of the joint fluid. Most authors mention the finding of blood in the cavity of the joint at operation, but not enough emphasis is placed on aspiration of joint fluids. The finding of hemorrhagic fluid without recent injury in conjunction with the bilirubin content of the effusion furnishes a conclusive diagnosis of hemorrhagic, villous synovitis. One of use (Kling<sup>18</sup>) has pointed out that a hemorrhage in the joint cavity is finally broken down to bilirubin. A high content of bilirubin is, therefore, proof of an older hemorrhage in the joint. In our case the icteric index was between 58.8 and 50 in subsequent aspirations, the normal content of bilirubin in joint fluids being below 5. This means a rise in the content of bilirubin in our case to about ten times the normal, proving that the aspirated blood originated from a spontaneous hemorrhage and was not due to a lesion of a vessel during aspiration. The almost constant level of the bilirubin in several aspirations showed that a constant bleeding was occurring into the joint cavity. A high content of cholesterol in the synovial fluid would establish the presence of xanthoma conclusively. The tissue in our case had the characteristics of the giant cell tumors. The synovia was much thickened, villous, hemorrhagic and in places yellowish owing to precipitation of lipoids. The sections showed that the villi were lined by several rows of synovial cells; the stroma contained large amounts of newly formed blood vessels, much blood pigment and giant cells. The high cholesterol content of the blood (288 mg. per hundred cubic centimeters of blood) months after the synovectomy indicated a primary disturbance of the lipid metabolism which led to the production of xanthoma in a joint weakened by occupational trauma or by some inflammatory factor.

---

18. Kling, D. H.: Bilirubin in Effusions of the Joints: Methods of Estimation and Significance, *Arch. Surg.* 20:17, 1930.

So far all the evidences are in favor of the benign character of these growths. Recurrences appear only when they are not removed entirely and then only in the synovial membrane. Early diagnosis is important in view of the continuous bleeding and growth of the lesion. The importance of early aspiration and examination of the synovial fluid is to be emphasized.

Operation should be performed as soon as the diagnosis is made and should consist of the removal of as much of the synovia as possible. In case a complete synovectomy cannot be performed it may be advisable to give deep radiation. The prognosis is favorable, but a possible recurrence must be considered. A check-up examination of our patient one year after the operation showed perfect motion of the knee joint and no recurrence of symptoms.

#### SUMMARY

1. Diffuse hemorrhagic villous synovitis due to xanthoma of the left knee joint was successfully treated by synovectomy. A year and a half after operation there was no recurrence of symptoms.

2. Repeated examination of the blood up to one year after operation showed a hypercholesteremia, indicating a primary disturbance of the lipid metabolism as the underlying cause for the precipitation of lipoids and the formation of the xanthoma.

3. A critical review of the reports of cases and the theories of pathogenesis of this rare condition is given.

4. The complete removal of the growth promises permanent cure. Early diagnosis is therefore of paramount importance and can be accomplished by careful examination of the joint fluid, and especially by the estimation of the bilirubin and cholesterol content of the effusion.

715 Wilshire Medical Building.

51 West Eighty-Sixth Street.

# CONGENITAL COXA VARA

ISADORE ZADEK, M.D.

NEW YORK

## INTRODUCTION AND REVIEW OF THE LITERATURE

The words varus and valgus, it seems, originally had an identical meaning signifying steep or oblique. Later a differentiation was introduced, so that varus now means a deformity in which the extremity distal to it bends toward the midline. Valgus has the opposite significance.

Isolated reports of coxa vara appear in the literature prior to the description given by Fiorani in 1881 of a group of fifteen patients whose disability he concluded was due to a change in the angle of the neck of the femur. It is difficult to judge in the present light just what cases were included, as he specifically stated that motion at the hips was normal in many of these cases. He mentioned the fact that several of the patients were children of consanguineous marriages. He suggested that improper food may have a bearing, which suggests that some of the cases may have been of rachitic origin. He described a typical caliper brace for support, which even included a ring at the top with a joint at the knee. One will appraise this report at its true value if one realizes that it appeared in 1881, some years prior to the discovery and use of roentgen rays.

In 1888 Müller again called the attention of the surgical world to a deformity of the femoral neck, with adduction of the distal part of the limb, which depressed the neck of the femur from the usual 125 to 130 degrees. The cases described were apparently instances of epiphyseal separation at the hip.

The name "coxa vara" was given by Hofmeister in 1894, and this appellation took root immediately. As I understand coxa vara, it is a depression of the neck of the femur, so that the angle which the neck of the femur makes with the shaft is less than the normal angle of 125 or 130 degrees seen in adults. Hence it approaches 90 degrees, or it may be less than 90 degrees. The deformity may be at the base of the neck, or nearer the head of the femur. One must realize also that the neck of the femur may not be in the same plane that passes through the condyles of the femur. Normally there is some anteversion of the neck of the femur, which may amount to as much as 20 degrees, according to Elmslie. In coxa vara, the neck of the femur may be depressed directly downward, or the greater trochanter may, with the base of the neck, be forward or backward.

Congenital coxa vara is obviously the most infrequent type. The literature on it, however, is more extensive than one would expect.

Congenital coxa vara was described by Kredel in 1896. In his cases and the cases described by earlier authors, there were other malformations, such as knock-knee, equinovarus or a defect of the patella. In Kredel's original report there were two cases, one in a child, aged 5 months, and the other in a child, aged 3 years. Attention was attracted to the first case by the peculiar position assumed. One hip was held in adduction and the other in abduction. This suggested to the author a lack of space in utero as a possible etiologic factor. The second child could not stand or walk. It is of interest that the author mentioned a limitation of abduction at the hip in these cases and considered it a point of differentiation from rachitic coxa vara. This one knows is not true. Coxa vara due to rickets shows the mechanical limitation of abduction.

Kirmisson, in 1897, reported the autopsies made on two infants, aged  $2\frac{1}{2}$  and 1 month, respectively. These included the hip joints, which showed what he considered to be congenital coxa vara. He found the greater trochanters to be much posterior and stated that this was due to the short posterior fibers of the capsule.

Mouchet and Aubion, in 1899, called attention to the fact that congenital coxa vara is not necessarily associated with other congenital anomalies. (Apparently the only cases recognized earlier were observed on examination incidental to the finding of the other obvious deformities.) These authors stated specifically that their cases of congenital coxa vara showed no signs of rickets.

Alsberg, in 1899, observed congenital dislocation of the hip on one side and congenital coxa vara on the other. He was the first to suggest that intra-uterine pressure may have been sufficient to cause a dislocation of the hip on one side and only enough to depress the neck of the femur on the other.

Reiner, in 1903, recognized congenital coxa vara as one stage of a rather extensive femoral defect and first suggested a theory as to its causation.

Hoffa, in 1905, described a case of bilateral congenital coxa vara in a boy, aged 4 years. A resection of both hips was performed in 1902. Hoffa considered that the developmental disturbance of the normal epiphysis was the cause of the deformity. A microscopic examination of the specimen was made, which will be referred to later. This is the first microscopic report of congenital coxa vara. Others have been made by Delitala and Barr. A specimen was removed by Nilsonne, who stated that a microscopic report (1928) would be made later. No record of this report could be found. In the discussion of Nilsonne's report Camnitz stated that four specimens were removed by him.

Hoffa suggested that a differentiation between rachitic and congenital coxa vara might be made on the direction of the epiphyseal line in the neck of the femur, as seen in the roentgen film, which he stated is vertical in congenital coxa vara and oblique in rickets, being oblique from above and outward, downward and inward.

Feiss, in 1906, reported a case of congenital coxa vara in a girl, aged 3 years. This was of the type originally described by Kredel. Here, dating from birth, the left lower extremity was held adducted into approximation with the right. Feiss quoted from Kredel, "When one has seen this well nourished and active child taking this position repeatedly, then one cannot doubt the fact that both legs had grown in this position in utero for a long period."

Francke, in 1906, reported congenital coxa vara in siblings. They were a boy, aged 6 years, and his two sisters, aged 5 and 2 years respectively.

Helbing, in 1906, suggested that congenital coxa vara is manifested in delayed or deficient ossification of the upper end of the femur.

Ghuilamila, in 1907, reported a case of congenital coxa vara (bilateral) complicated by tuberculosis on one side. This diagnosis of tuberculosis was based on clinical and roentgen findings.

Frisch, in 1908, reported a case of bilateral congenital coxa vara in a girl, 7 years of age. He stated that up to that time about thirty cases had been described in the literature.

Rafilsohn, in 1908, reported two cases of congenital coxa vara and stated that congenital dislocation of the hip had been observed on one side and congenital coxa vara on the other.

Spitzzy, in 1909, stated that there was no causal connection between congenital coxa vara and congenital luxations, but that coxa vara associated with a luxation is, as a rule, of secondary origin.

Drehmann reported a case of congenital coxa vara in a girl of 16, in whom he reported raising the angle of the neck of the femur to 120 degrees from 65 degrees by stretching the hip into full abduction. The defective portion of the neck gave way under tension, permitting the correction. A plaster of paris spica was left on for five months. Later a fixed abduction deformity was corrected by a simple osteotomy; Drehmann stated that the functional result was highly satisfactory.

Mayer, in 1910, reported a case of bilateral congenital coxa vara in a twin, aged 24. The patient showed a greater angle of the neck of the femur on the right side than on the left. The complaint of disability was greater on the right side. Mayer called attention to the fact that the disability was due to extra-articular strain on the capsule, muscles and the like. Owing to atrophy of the neck of the femur, Mayer stated, the head of the femur looked like a mushroom or like the head of a giant placed on the neck of a dwarf.

Delitala, in 1913, reported a case of congenital coxa vara of the left side in a child of 3 years on whom a subtrochanteric osteotomy had been performed. One month after the operation the child died of pneumonia. At postmortem examination the muscles, capsule and ligaments of the hip were found to be normal. Histologic examination of the head and neck of the femur was made.

Schwarz, in 1913, reported three cases of congenital coxa vara. In each case the patient began to walk at about 15 months of age. In one patient observed at the age of 4 years there was a defect in the neck of the femur with the commonly seen area of transparency shown in the roentgen films. Eleven years later the defect had spontaneously disappeared, and in its place there was well developed bony tissue.

Elmslie, in 1913, in reviewing coxa vara in general designated congenital coxa vara under the title of infantile coxa vara. He described a gross specimen which had been removed by Robert Jones from a woman, aged 26, and another which he found in the museum of St. Bartholomew's Hospital. The hips from both patients were preserved. The defects were accidentally discovered in the dissecting room.

Following Elmslie's designation of infantile coxa vara, Perrier, in 1914, reported a case of congenital coxa vara observed by Nove-Josserand at autopsy in an infant dead at birth. Congenital coxa vara and dislocation of the hip were coexistent.

Brand, in 1916, mentioned the important fact that the prognosis in congenital coxa vara is entirely dependent on whether or not ossification occurs in the defect in the neck of the femur. Failure of union to materialize fully predisposes the patients to a fracture of the neck of the femur in later life, with resulting nonunion and pseudarthrosis and with the marked displacement and absorption of the useless femoral head involving serious disability.

Lepoutre, in 1921, reported a case of right-sided congenital coxa vara with absence of the patella on this side. The child was 6½ years old. Lepoutre expressed his belief in an unjustifiably hopeless outlook.

Nilsonne, in 1924, suggested that the anomaly of ossification may be basically due to an embryonic vascular disorder. In 1928 he reported bilateral congenital coxa vara in a girl of 7 years, who died of tuberculous meningitis. He stated that there was defective ossification with an irregular epiphyseal line, and that several islands of cartilage were found in the epiphysis and the metaphysis.

In the discussion Canitz stated that he removed four femoral heads from patients with congenital coxa vara and examined them histologically. No epiphysis was found. Cartilage of different kinds and islands of bone and connective tissue were lying about in profusion.

Noble and Hauser, in 1926, published an excellent review of coxa vara in general, including also the congenital type. They stated that operations on the necks of the femurs in the congenital type were frequently disastrous, and that nonunion might ensue. They presented roentgen films of a man with congenital coxa vara and nonunion of the neck of the femur and also showed the roentgen appearance ten years previously with a typical attenuated neck.

Fairbank, in 1927, reported a case of congenital coxa vara and showed a roentgen film. There appeared to be no neck. (It was supposed that the neck was present but unossified.) The child was  $3\frac{1}{2}$  years of age. There was a shortening of  $4\frac{1}{2}$  inches on the affected side. Practically all of the shortening was in the femur. It was proposed that an osteotomy be done later to correct the deformity. The child died suddenly at operation. Death was due to massive pulmonary thrombosis. The specimen showed that the defect in the neck of the femur was non-existent. In this location there was cartilaginous tissue.

Fairbank presented a rather complete review of the subject in 1928.

Peabody, in 1927, reported in full a case of typical congenital coxa vara (bilateral) in a woman, aged 23.

Jansen, in 1929, suggested that pressure in utero on the flexed knee in the axis of the femur may have a bearing on congenital coxa vara (coxa fracta).

Barr, in 1929, reported five cases of congenital coxa vara with a histologic report of a specimen removed from one of the patients. The other patients were not operated on.

Kreuz, in 1930, discussed congenital coxa vara and reported the case of a child whose roentgen findings presented an epiphyseal line in the neck of the femur that at first was vertical, but which three years later was slanted. He therefore felt that this disproved Hoffa's suggestion that the epiphyseal line is vertical in the congenital form of coxa vara in contradistinction to the other forms.

Bargellini reported a case of bilateral congenital coxa vara followed clinically and roentgenologically for a period of twelve years. The child was seen from the age of 4 years to the age of 16. The deformity was marked on one side. On the other side it was mild. On the more markedly involved side it progressed to separation of the epiphysis. On the less marked side there was healing with anatomic and functional cure under conservative treatment. The more involved side, on which the condition progressed to nonunion, was operated on at the age of 16.

Sacerdote, in 1931, showed a girl, aged  $4\frac{1}{2}$  years, with congenital dislocation of the right hip and congenital coxa vara of the left hip of 90 degrees. This was confirmed by roentgen findings. The right hip was easily reduced under anesthesia. Six months later a subtrochanteric

46563

osteotomy of the left hip was performed. Nine months after operation a normal osseous structure of the head and neck was found, with the angle of the neck at 120 degrees. The epiphyseal line had practically disappeared.

#### ETIOLOGY

As in other congenital anomalies, any suggestions as to the cause of coxa vara that one finds at birth are purely theoretical.

Alsberg, in 1899, suggested that intra-uterine pressure may account for the congenital coxa vara.

Helbing felt that there was perhaps a fissure with a lack of proper ossification in the neck of the femur. He felt that there may be an abnormal anlage which came to expression in postfetal life.

Reiner also suggested intra-uterine pressure as having an important bearing on the condition. He stated that at about the tenth week of fetal life the normally abducted and flexed femur becomes adducted, and at this time an angle is formed between the neck and the shaft of the femur. Pressure of the membranes may cause a complete obliteration of the bone at the hip. Less pressure may cause only congenital coxa vara.

Hoffa made almost the same suggestion, that because of intra-uterine pressure the neck of the femur loses its property of growth.

Drehmann followed out much the same idea and considered the abnormal zone in the neck of the femur simply a defect of the first degree. A more marked defect may indicate the absence of a variable portion of the upper portion of the femur.

Nilsonne, in 1924, suggested that the anomaly of the neck of the femur may be due to an embryonic vascular disturbance.

#### MICROSCOPIC APPEARANCE

The microscopic appearance of bone removed from the affected portion of the neck of the femur shows nothing characteristic.

The description of a gross specimen was given by Elmslie:

The specimen resected by Mr. Robert Jones from a woman, aged 26 years, in whom both hips were affected, and whose symptoms dated from birth, shows very well the condition finally attained (Royal College of Surgeons Museum, Specimens 1785d and e). The head of the bone is displaced downward, so that only a narrow interval remains between it and the shaft, the neck pointing downward and inward. The lower part of the head, neck and shaft are continuous, with, however, a fine fibrous intersection between them; above this a clear line of fibrous tissue separates the head and the adjacent part of the neck on the inner side from the root of the neck on the outer, a separated area of bone of a different texture, and a space containing fibrous tissue existing here also. The Museum catalogue says: "The appearances, therefore, indicate that a solution of continuity has taken place between the neck and the head close behind the latter,



that osseous union has followed between the opposed lower portion of the neck and the head (?), and that a formation of callus has occurred upon the exposed surface of the neck and occupies the interval between this and the higher part of the head."

This was evidently a case of congenital coxa vara which had progressed to nonunion of the neck of the femur.

Elmslie reported another gross specimen which he found in the museum of St. Bartholomew's Hospital.

Nilssonne published the description of a gross specimen from a child, aged 7 years, who died of tuberculous meningitis.

Neither of these cases was accompanied by a report of a microscopic examination.

Hoffa reported that:

A section including the entire width of the head and neck of the femur and part of the adjacent femur itself was microscopically examined. The cartilaginous portion of the specimen consisted almost throughout of permanent cartilage, which was highly vascularized in several spots. Among the sanguineous capillaries there was very loose connective tissue with small foci of extravasation. Near these vascular islands the basic cartilaginous substance was more fibrous. There was nowhere any indication of proliferating cartilage. Near the center of ossification of the head of the femur there were irregular nodules of cartilage, whose capsules stained deeply with hematoxylin and showed granular calcification. This zone showed no indication of cartilaginous proliferation. The nodules showed occasionally a few isolated spicules of bone. At the periphery of the nodules the cartilage was transformed into fibrous connective tissue. Nearer the center of ossification the fibrous transformation of the cartilage was more extensive. At a small circumscribed spot the cartilage was necrotic and invaded from all sides by very cellular connective tissue. The periphery of the cellular layer adjacent to the necrotic cartilage showed also isolated, rounded and multinuclear giant cells. The spicules of bone were extraordinarily irregular. They showed absolutely no conical arrangement in the direction of the cartilage. Only a very few and isolated spots showed a border of uniformly directed cells interpreted as osteoblasts. The medullary spaces had very few cells and abundant fat. Vascularization was poor. Occasionally the marrow was transformed into fibrous connective tissue with few cells. The periosteum also showed no cell proliferation or transformation into bone spicules.

The report by Delitala in 1913 follows:

*Histologic Examination.*—For the histologic examination I employed a slice taken from the centre, including the whole section decalcified by Schafer's method, and stained with haematoxylineosin, with carmin, and Schmorl's method number two. For the sake of clarity I shall divide the description into three parts: (1) the part concerning subtrochanteric osteotomy and the line of the callus; (2) the part dealing with the neck of the femur together with its bony part, its conjugate cartilage, and the zone of ossification which lies between; (3) the part that refers to the head of the femur and that is the least interesting.

As regards the osteotomy, we find that the corticals of the diaphysis incuneata and of the two trochanters are joined together by abundant bone trabeculae run-

ning obliquely and circumscribing areas of medullary tissue of the fibrous type: the ossification of the callus has proceeded according to the normal type in man and in such a way as to secure good union between the stumps.

In the neck of the femur we find an anomalous spongy tissue.

In the bone marrow of the femoral neck we do not find the typical young tissue corresponding with the age, but a marrow with numerous adipose elements and with extensive haemorrhages. Furthermore, it is not rare for it to contain cartilaginous nodules which, because they are of the same type as the conjugate cartilage, must be interpreted as the latter's remains not ossified and dislodged by the formation of the surrounding laminae of bone.

The cartilage of growth is formed by a hyaline (tissue) of very small cells, where the zone of repair is more extensive than any other: the region of proliferation shows capsules containing two, three, and more nuclei, but here, too, as opposed to what normally happens, the daughter cells stay small and have an oval nucleus which is very regular and stained heavily and homogeneously: at the edge of the diaphysis there is a thin and noncontinuous layer of cartilage with columns, but with elements of the same type, without any sign of decomposition of the cartilaginous cells; and the fundamental substance does not show that impregnation of calcium salts which is revealed in the region of normal ossification.

But still more notable is the fact that in its midst there are serpiginous, invading vascular areas where a capillary with numerous lateral buds is surrounded by a dense connective tissue, soft and spindle-shaped; the presence of the areas cannot be attributed to the oblique direction of the section. The finding is comparable with the figure which Axhausen gives of the vascular resorption of the cartilage in articular transplants. In some sections it is possible to follow one of these vascular plugs which excavates a canal from the diaphyseal surface of the conjugate cartilage up to the epiphyseal surface and thus connects the medulla of the nucleus of the head with that of the neck, yet without the slightest sign of formation of bone substance along its margins, either.

As for the zone of ossification, in addition to the zone already mentioned in regard to the stratum of the cartilage with columns which is deep down and at rest, because the capsules are not broken, its cells do not recede, its substance is not calcified, the irregularity of the course must be noted: instead of constituting a line that is almost regularly rectilinear and oblique with respect to the horizon, perpendicular with respect to the axis of the neck, it forms an almost horizontal streak shaped like a wreath.

Along it the endochondral ossifications take place slowly and are not continuous: after stretches in which slender trabeculae of bone are seen outlined along the cartilage in series come others in which the medulla approaches the cartilage without giving any signs of activity.

This finding explains to us the reason for the presence of cartilaginous nodules right in the ossified zone. The active zones, advancing just behind the inert ones, end by leaving the latter heterotopic, so that it is not necessary to resort to occurrences of metaplasia or something else to explain them.

What must be considered as the principal fact shown by the histologic finding, it seems to me, is the anomalous constitution of the conjugate cartilage, with which are connected the altered direction of the line of ossification, the slowness of the bone transformation, and the irregularity of form and arrangement of the spongy trabeculae: they are all facts which together account for the deformity of the neck of the femur and which I shall call dystrophic.

Barr reported the microscopic appearance of a specimen from one of his cases:

Six sections were made of the fragment of tissue received, which were composed of bone cartilage, fibrous tissue and muscle. Portions of the bony fragments showed the usual bone spicules and bone marrow. In three sections there was an alteration in the histology from that found in normal bone. The cartilaginous junction with the bone spicules was rather abrupt. The cartilage cells did not assume the linear arrangement nor the enlargement usually found along the line of ossification. The invasion of cartilage by blood capillaries was entirely absent. The marrow space in these sections ended abruptly at its junction with the cartilage. Cartilage was similar in appearance to that found in the articular surface. The cartilage in one area was found to be intimately united with bone spicules rather deep in the spongy bone. Islands of disintegrated cartilage were also found between the bone spicules. Some of the spicules showed evidence of faulty laying down of bone matrix and some atrophy of bone. Nowhere was there marked evidence of bone formation, nor was there evidence of repair. Owing to the fragmentary character of the tissue, the exact relation of this cartilage to the surrounding bone could not be determined. The histology was not sufficiently characteristic to permit a definite diagnosis as to the cause of the bone change. Somewhat similar changes are sometimes found in bones of animals in which there is a vitamin deficiency, other than those which are known to influence the laying down of normal bone.

The report, by Dr. H. L. Jaffe, pathologist at the Hospital for Joint Diseases, of a segment removed by me from the superior border of the neck of the femur of a patient, aged 5 years, follows. The segment included a portion of the articular cartilage and neck of the femur down to the greater trochanter.

Section of the larger piece, which revealed the articular cartilage, showed degenerative phenomena in the deeper layers of the cartilage with areas suggestive of mucinous degeneration and also the appearance of tiny intracartilaginous cysts, apparently on the basis of liquefaction of the cartilage. The subchondral bone was compact, there being widespread subchondral osteosclerosis, which extended through the entire capital epiphysis from the area from which the section was taken. Between the thick trabeculae there was a rather loose connective tissue containing vessels, osteoblasts on the surfaces of the canals and, in places, osteoclasts. Between the thick trabeculae areas of marrow were observed; in some regions the marrow showed an increase in the connective tissue stroma and also slight evidence in places of connective tissue bone formation. What was observed of the epiphyseal cartilage plate was extremely difficult to interpret, since it was at the edge of the section, the surgical specimen apparently passing through areas of the plate. The epiphyseal cartilage plate showed changes which might be interpreted as evidence of beginning closure. These changes extended down toward the neck, where the bone was sclerotic. An occasional islet of included epiphyseal cartilage plate was observed within the substance of the bone. Another fragment of bone, apparently from the neck, showed considerable compact sclerotic bone with fragments of the epiphyseal plate and other fragments of epiphyseal cartilage plate within the substance of the epiphysis.

Specimens of the defective portion of the neck of the femur from three other cases of congenital coxa vara have been removed and examined at the Hospital for Joint Diseases. They are referred to in the individual case reports.

#### HISTORY AND PHYSICAL FINDINGS; DIFFERENTIAL DIAGNOSIS

The deformity and painless limp are the striking signs in these cases in childhood.

Pain begins in adolescence or adult life if the patient is not treated; if the neck has given way with resulting nonunion, the disability is marked, so that the patient seeks relief.

Examination shows all of the cardinal signs of coxa vara: a limp; elevation of the greater trochanter; limitation of abduction; sometimes

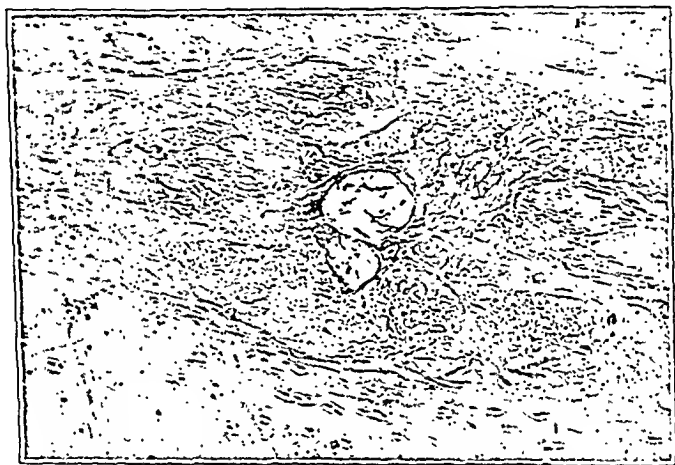


Fig. 1.—Photomicrograph showing microscopic cyst in the articular cartilage.

internal rotation; more rarely, external rotation; a positive Trendelenburg sign, and the head of the femur palpable beneath the femoral artery in the groin. If the condition is bilateral, a markedly increased lumbar lordosis is present.

In contrast to the cases reported in the early literature in which other congenital anomalies were associated, the cases which I am here reporting showed no other anomalies.

The children begin to walk tardily, as a rule about the fifteenth month or later, and it is then that a peculiar gait is observed. The history is not characteristic, and it could be readily confused with congenital dislocation of the hip. The gait may not make sufficient impression on the parents at this early date, and several years may intervene before the child is brought for medical attention, though the

majority of cases at the present time, owing to better education of the masses by medical men, are seen early.

There may be a history of injury, but more careful questioning will disclose the fact that the condition antedated the injury, and that the injury was not severe enough to have initiated the condition. The added disability after the injury is likely to be transient, though it may suffice to focus attention locally.

If the condition is bilateral, the increase in the lumbar lordosis is more striking, and the resemblance to congenital dislocation of the hip is more striking, especially with the presence of a waddling gait.



Fig. 2.—Photomicrograph showing the irregular distribution of the cartilage cells in the epiphysis.

On physical examination the greater trochanter is found to be elevated and prominent. The greater trochanter is apparently usually posterior to its common position, and there may be a fixed flexion deformity at the hip in the older cases. In contrast to congenital dislocation of the hip, the head of the femur is found in a more or less normal position with relation to Poupart's ligament, and when force is applied in the axis of the femur and relaxed alternately, the hip does not "pump" or "telescope." Because of the lack of proper balance at the hip, Trendelenburg's sign is present, and even after correction of the depression of the neck of the femur, with restoration to nearly normal,

this sign may remain positive. This is no doubt influenced by a shortened neck, whether or not it is the result of operative intervention.

Unless there are secondary changes about the hip joint, influenced by the development of a superimposed arthritis, there is no muscle spasm or other evidence of an acute condition. There is no local sensitiveness.

There is limitation of motion, but this limitation of motion is, without secondary changes, entirely mechanical. One therefore expects limitation of abduction, and this may be slight or great, depending on the degree of depression of the neck of the femur and its impingement



Fig. 3.—Photomicrograph showing an island of cartilage surrounded by bone. In areas the surrounding bone is dense.

against the rim of the acetabulum or the striking of the greater trochanter against the side of the ilium in forced abduction. Shortening of the soft parts, particularly in the older cases, will limit motion. This is especially true of the adductor muscles of the thigh and the portions of the capsule, particularly the posterior part.

#### ROENTGEN APPEARANCE

The roentgen appearance of these cases is most interesting, and unless one is familiar with it, the proper diagnosis will not be made. The obvious thing is the depression of the neck of the femur. As one

looks more closely, there seems to be loss of substance in the neck, which to the uninitiated immediately suggests a fracture with resulting nonunion. The epiphyseal line in these cases, as first mentioned by Hoffa, is vertical, with a branching, usually at its inferior portion (though it may be superior) like an inverted Y enclosing bone between its two arms. This defect is much wider than the normal epiphyseal line.

(Fractures of the neck of the femur in infants and children are uncommon. They require severe trauma for their production. They are usually of the hinge type at the base of the neck and heal readily.)

The greater trochanter is elevated, and in the older cases it becomes much elongated and takes on a "beaked" appearance. It may be in contact with the ilium.

In the adolescent this defect in the neck of the femur may give way completely, and resulting nonunion may be truly present, with no contact between the head fragment and the contiguous portion of the neck of the femur, or there may be fibrous union. The shaft may then be displaced upward, so that the head fragment may be at the level of the lesser trochanter.

The head of the femur occupies the lower portion of the acetabulum and is often partially below the lower rim. Later it becomes more or less depressed from the acetabulum and appears to be near to, or in contact with, the lesser trochanter. In some cases of this sort the head is much larger than the attenuated neck, and no better description of the relationship can be given than that of Mayer, who said that the head was mushroom-shaped, appearing like the head of a giant on the neck of a dwarf.

The acetabulum may show considerable change in outline. It is shallow and defective in its inferior portion, owing to pressure from a relatively large head of the femur, which is low in its relationship to the acetabulum. At times shadows are seen in the acetabulum suggestive of osteochondritis.

#### PROGNOSIS

The prognosis is governed entirely by what happens in the neck of the femur where defective ossification is present. If the condition is mild, according to reports, ossification may proceed uninterruptedly. Unfortunately, this is not the usual happy outcome. If this were true, one would be justified in waiting for complete ossification and then correcting the coxa vara. Without surgical intervention the condition tends to become progressively worse, and in untreated patients to result in separation of the head of the femur and nonunion. At this stage there are secondary arthritic changes, with pain and great disability.

## TREATMENT

The older writers held a rather hopeless and more or less helpless view of these cases. The patients were treated by forced abduction in traction or plaster of paris dressings.

The line of treatment should have two definite goals, both attained by surgical intervention.

1. The defect in the neck of the femur should be overcome by an operative opening up of a new blood supply, preferably through drilling the neck of the femur. This means obliteration of the epiphyseal line. In several of the cases reported here this was accomplished by different surgical procedures, such as the insertion of a beef-bone peg, the insertion of an autogenous peg and the removal of a disk of bone from the neck.

Operations directly on the neck in these cases are attended by more than the usual risk of infection because of the defective tissue with an inadequate blood supply. The drilling from below the greater trochanter into the neck seems to be the simplest procedure.

2. After the neck has been sufficiently ossified, a wedge osteotomy of the subtrochanteric type should be done to restore the angle of the neck of the femur.

I feel that these procedures should be carried out when the patients are first seen, that is, from about 3 years on.

A reconstruction operation, such as the Whitman or Brackett type, should be reserved for older untreated patients with nonunion. If proper operative care is given early, few, if any, reconstruction operations will be necessary.

## REPORT OF CASES

CASE 1.—E. R., a white girl, aged 7 years, was breast fed for fifteen months. The family history and the patient's history were unimportant. The birth was normal. There was no history of injury. The patient walked alone at 16 months of age.

The child was brought to the Hospital for Joint Diseases in October 1927, because of a limp and shortening of the left lower extremity. When she was 3 years old, her mother noticed that she limped. She was treated in another institution by the application of a plaster of paris spica, which was worn for six months. This resulted in no improvement. The condition progressed. The patient could walk a considerable distance without fatigue. There was no history of injury to the hip.

General examination gave negative results. The patient walked with a limp on the left side. The only motion limited at the left hip was abduction, which could be carried out to 10 degrees as compared with a normal range on the right.

Measurements showed that the distance from the anterior superior spine of the ilium to the internal malleolus on the right (which will be designated as R.A. in the remaining cases) was  $24\frac{1}{4}$  inches.



The distance from the anterior superior spine of the ilium to the internal malleolus on the left (which will be designated as L.A.) was 23 inches.

The distance from the umbilicus to the internal malleolus on the right (which will be designated as R.U.) was 26 inches.

The distance from the umbilicus to the internal malleolus on the left (which will be designated as L.U.) was 25 inches.

The circumference of the right thigh (which will be designated as R.T.) was  $13\frac{1}{4}$  inches.

The circumference of the left thigh (which will be designated as L.T.) was  $13\frac{1}{4}$  inches.

The circumference of the right calf (which will be designated as R.C.) was 10 inches.



Fig. 4 (case 1).—Showing left congenital coxa vara.

The circumference of the left calf (which will be designated as L.C.) was  $9\frac{1}{2}$  inches.

The Wassermann reaction was negative.

The roentgen examination on November 8 showed a normal hip on the right side. On the left there was coxa vara of 80 degrees. The head of the femur was relatively large and low in the acetabulum, being partially out of the inferior border of the acetabulum. The epiphyseal line of the neck was widened and vertical. The acetabulum was flattened.

A subtrochanteric wedge osteotomy was performed on November 9. A 5 inch incision was made over the lateral aspect of the left femur, exposing the upper part of the shaft. The tissues were stripped back until the trochanter and neck and a little of the head of the femur were exposed. The deformity of the neck was clearly demonstrated. A specimen of bone running through the neck and head was removed for microscopic examination. Then a wedge of bone, measuring

three-eighths inch at its base, was removed from the intertrochanteric line. It was then possible to abduct the hip to 35 degrees. After closure of the wound a plaster of paris spica was applied in this attitude.

A microscopic examination of tissue removed from the head and neck of the femur was made by Dr. H. L. Jaffe. It showed no characteristic lesion of the bone.

The patient was readmitted to the Hospital for Joint Diseases, and the plaster of paris spica was removed on Jan. 4, 1928. The spica was bivalved, and the extremity carefully removed from it. At the site of osteotomy the bone was solid.



Fig. 5 (case 1).—Appearance after subtrochanteric wedge osteotomy of the left hip. A specimen of bone was taken from the neck of the femur at the time of operation. Roentgen examination was made through a plaster of paris spica.

The trochanter rotated with the shaft. The hip showed a range of motion of about 10 degrees in all directions.

Physical therapy was instituted, and the child was allowed to walk with crutches.

Examination on Nov. 28, 1932, showed the following: The patient was satisfied with the result of her operation. She was as active as other girls and had no pain. She was in good condition. She walked with a slight limp and had a positive Trendelenburg sign on this side. There was a slight increase in the lumbar lordosis, with slight increase in the dorsal kyphosis and forward inclina-

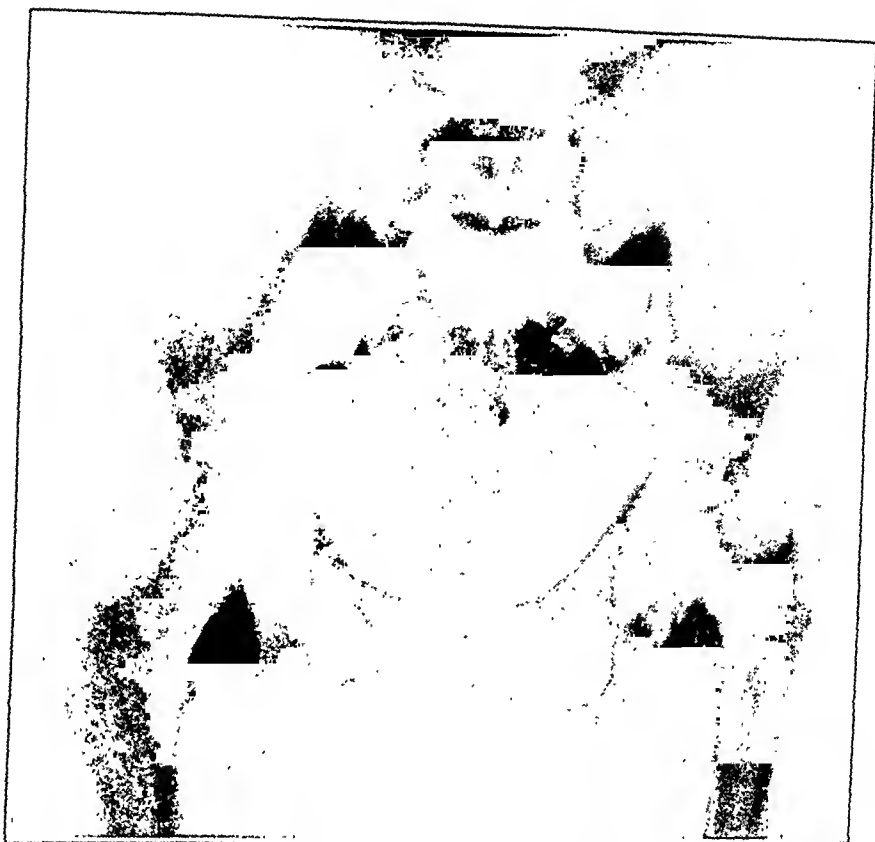


Fig. 6 (case 1).—Appearance five years later. The coxa vara has been corrected, and most of the neck of the femur has disappeared. There is bony union of the remaining portion of the neck with restoration of the angle of the neck.

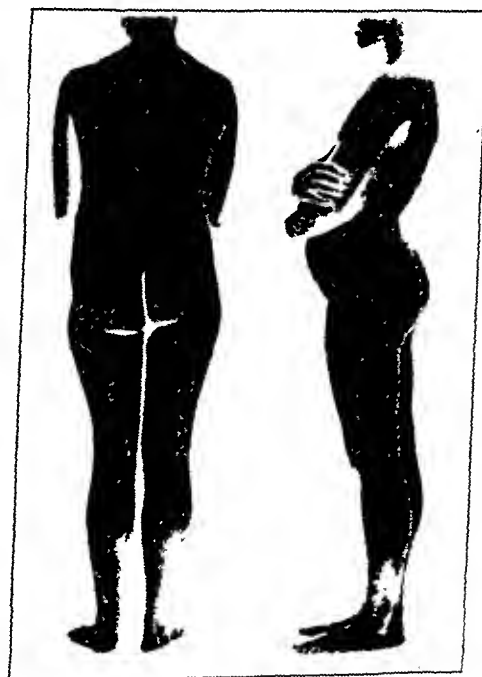


Fig. 7 (case 1).—Appearance five years after operation. The lumbar lordosis is slightly increased.

tion of the head and neck to a moderate degree. The greater trochanters were slightly posterior to the shoulders. The general posture, however, was satisfactory. The pelvis was tilted down slightly on the left. There was no spasm of the spinal muscles. The flexibility of the spine was normal. There was no sensitiveness over any part of the spine, the sacro-iliac joints or the gluteal muscles. There was an incision over the lateral aspect of the left hip beginning at the level of the base of the greater trochanter, which showed no reaction about it. The left hip was in almost complete extension and in moderate abduction. Flexion at the hip was normal. Adduction was normal. Abduction of the left hip to 30 degrees, as compared with 45 degrees on the right, was permitted. Rotation of the left hip was



Fig. 8 (case 2).—Congenital coxa vara of the right hip.

normal. The internal rotation of the right hip seemed slightly greater than normal. The patellas were normal. There was no deformity of the feet. Measurements showed: R.A.,  $31\frac{3}{4}$  inches; L.A.,  $30\frac{3}{4}$  inches; R.U.,  $33\frac{1}{2}$  inches; L.U.,  $33\frac{1}{2}$  inches.

CASE 2.—H. B. was a white boy, aged 7 years. His history and that of the family were unimportant. The histories were obtained from his foster mother, who had cared for him for three years. When she took charge of him he was walking with a limp on the right side, and it was reported that there was a shortening of one-half inch. This shortening gradually increased. One year before admission it was 1 inch. The limp became more marked.

The patient was admitted to the Hospital for Joint Diseases on Sept. 17, 1929, with a shortening of the right lower extremity and a limp.

The general examination gave negative results. Orthopedic examination on admission showed that the patient was in good condition. He walked with a limp on the right side. The greater trochanter on this side was elevated and prominent. It was above Nélaton's line. There was a positive Trendelenburg sign on this side. Abduction was completely restricted. Measurements showed: R.A., 19¾ inches; L.A., 21 inches; R.U., 22¾ inches, and L.U., 24 inches. R.T., 11¼ inches; L.T., 12½ inches; R.C., 8½ inches, and L.C., 8¾ inches.

Roentgen examination on admission showed that the left hip was normal. The right hip showed a coxa vara of 75 degrees. The epiphyseal line, which was vertical, was much widened and branched in its inferior portion. The large head



Fig. 9 (case 2).—Appearance six weeks after operation (subtrochanteric osteotomy and insertion of an autogenous bone graft through the trochanter and into the head). The displacement is that of a bifurcation operation. The defective tissue in the neck of the femur has been removed, and the neck has thereby been shortened. This roentgen examination was made after removal of the plaster of paris spica applied at operation.

was subluxated inferiorly from the acetabulum. The acetabulum was somewhat irregular in its lower half and flattened.

On September 25 a cervical osteotomy and bone graft were done. A 3 inch incision was made over the adductor muscles of the right hip. These muscles were freely divided, and the muscle stumps were sutured. The wound was closed with a continuous plain stitch.

An 8 inch incision (modified Smith-Petersen incision) was made, the lower end of which curved backward, exposing the trochanter. The fibers of the capsule of the hip joint were incised longitudinally, and the neck freely exposed. Its gross appearance was normal except for the marked downward angulation and a slight amount of anteversion. With a Putti hip chisel the neck was divided transversely at the point of most marked angulation. Some difficulty was experienced in dividing the cortex on the posterior surface. After division it was possible to abduct the hip freely, but a gap remained between the fragments until the shaft was rotated internally. To maintain the shaft in this position, it was decided to insert a bone graft.

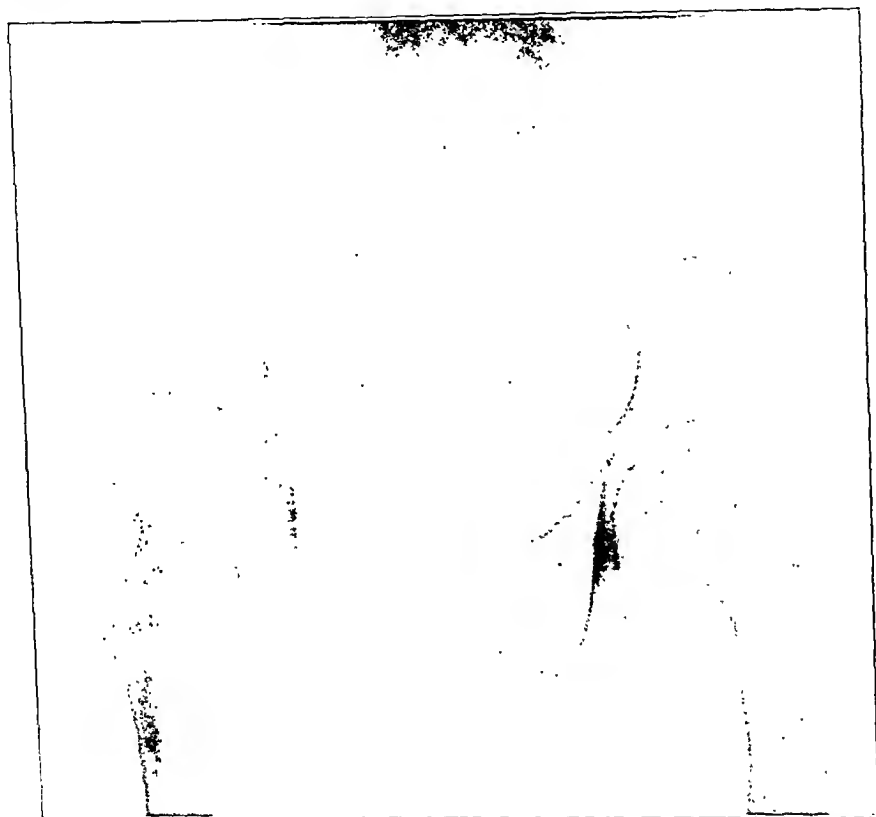


Fig. 10 (case 2).—Appearance two years after operation. The deformity has been corrected, and the head of the femur is higher in the acetabulum. Union is solid.

A 3 inch incision was made directly over the anterior surface of the tibia on the right side. A bone graft, measuring  $2\frac{1}{2}$  inches in length by  $\frac{1}{4}$  inch in thickness, was rapidly removed with an Albee saw. A drill hole was passed from the trochanter into the neck and head, and into this the bone graft was driven, jamming the two bone surfaces against each other. The extremity was immobilized in extreme abduction, and moderate external rotation in a plaster of paris spica, extending from the axilla to the toes.

The operative incision subsequently showed a mild infection.

The report of the tissue removed from the neck of the femur was made by Dr. H. L. Jaffe, who found nothing characteristic in the microscopic picture.

Examination on June 9, 1931, showed that the patient walked with a scarcely perceptible limp on the right side. There was excellent stability of the right hip. There was a marked keloid formation over the anterior aspect of the hip. The right hip was in full extension and could be flexed to 70 degrees. Abduction of the right hip was permitted to 45 degrees and adduction to 30 degrees.

Measurements showed: R.A.,  $22\frac{1}{2}$  inches, L.A.,  $23\frac{3}{8}$  inches.

The patient was able to indulge in the activities of other boys of his age.

No recent examination has been made of the patient, as he moved to a distant city and we were unable to secure a report of his present condition.

CASE 3.—V. C., a colored boy, aged 7 years, was brought to the outpatient department of the Hospital for Joint Diseases on March 7, 1932, because of a limp on both sides and hollowness of the back. Birth was normal. The patient's

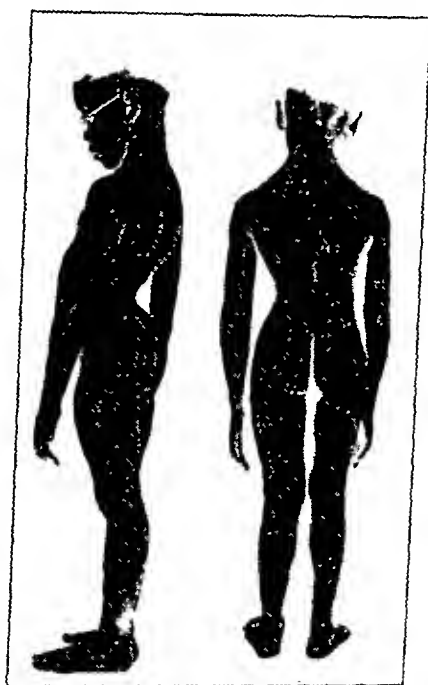


Fig. 11 (case 3).—Marked lumbar lordosis.

history and the family history were unimportant, except that the mother stated that the boy fell from a shelf above the sink in July 1931. There was some discoloration over the right hip, but the patient did not complain of pain, nor did he limp immediately afterward. He walked at the age of 14 months.

Physical examination on March 23, 1932, showed that the patient was in good general condition. He walked without assistance, but he had a distinct waddle, suggestive of a bilateral coxa vara or congenital dislocation of the hips. The back was symmetrical, but there was a marked increase in the lumbar hollow. The patient presented marked flat feet. In the supine position the lumbar hollow was practically completely gone. The chest and the upper extremities were uninvolved, except that there was slight thickening of the wrist joints.

In the right lower extremity at the hip joint flexion was complete; extension was complete; abduction was checked at an angle of about 20 degrees; adduction was entirely free; inward rotation was slightly limited, and outward rotation was

somewhat restricted. At the knee and ankle joint there was no limitation of motion. The heads of the femurs were in the acetabula.

In the left lower extremity extension and flexion were free. Abduction was limited to 10 degrees; inward rotation was slightly limited, and outward rotation was somewhat restricted. At the knee and ankle joint there was no limitation of motion. Measurements showed: R.A.,  $23\frac{1}{2}$  inches; L.A.,  $23\frac{1}{2}$  inches; R.T., 13 inches, and L.T.,  $12\frac{3}{4}$  inches. The Wassermann reaction was negative.

Roentgen examination made on admission showed a bilateral coxa vara of approximately 90 degrees on both sides. There was a marked defect in the neck of the femur on both sides with attenuation of the bony substance. This was more marked on the left side. There was upward displacement of the trochanters. The epiphyseal lines of the necks of the femurs were widened and branched at



Fig. 12 (case 3).—Bilateral congenital coxa vara.

their inferior borders. The heads of the femurs were low (subluxated), and the acetabula were irregular in outline.

On admission an operation, which consisted of the removal of a specimen from the neck of the femur and the insertion of an ivory peg through the head and reconstructed neck of the femur, was performed on the right hip.

The hip was exposed through a "U" incision, with its convexity downward. The exposure was made between the tensor fasciae femoris and the gluteus medius. The greater trochanter was chiseled free in order to lengthen the neck of the femur. The capsule was thickened; there was no excess of synovial fluid, and the neck was adherent throughout to the capsule. The ligamentum teres femoris was apparently normal. The head of the femur was dislocated from the acetabulum by the operator; it was irregular in shape in the lower half and was much larger than the contiguous portion of the neck, corresponding with its roentgen appearance. A section of bone, including the attenuated portion of the neck, was removed. This was from one-half to three-fourths inch in thickness and contained hyaline cartilage. Considerable difficulty was experienced in cutting through the inferior



posterior part of the neck. The capital epiphysis was placed on a rounded portion of the base of the neck after several drill holes had been made into the capital epiphysis. The epiphysis was fixed to the reconstructed neck by driving an ivory peg from the fovea down through the neck. So little neck remained that it was reattached practically at the base of the greater trochanter. The greater trochanter was sewed lower down on the shaft of the femur by means of chromic catgut. A plaster of paris spica was applied, extending from the upper part of the chest to the toes, with the hip in 60 degrees of abduction and full extension, with the knee slightly flexed and the foot at a right angle.



Fig. 13 (case 3).—Appearance after operation on the right hip. The bone peg holds the epiphysis in contact with the neck, after a segment has been removed through the involved portion of the neck.

Following operation pyemia with foci in the left hip, the soft parts of the right elbow and the soft parts of the left arm developed. The patient survived, but with ankylosis of the hips.

Dr. H. L. Jaffe examined the tissue removed from the neck of the femur at operation and reported nothing specific on which to make a diagnosis.

CASE 4.—R. L., a white girl, aged 18 months, was brought to the Hospital for Joint Diseases because of a deformity and shortening of the left lower extremity associated with a limp on this side. She had been walking for six weeks, and the

limp had been apparent since she began to walk. She was admitted to the hospital on Nov. 13, 1929, for the correction of the deformity. The family history was unimportant. The child was premature (8 months). She was breast fed for eleven months.

The child was in good condition. She walked with a limp on the left side. The greater trochanter on the left was elevated and prominent. It was three-fourths inch above Nélaton's line. There was anterolateral bowing of the femur. The left hip could be abducted to 20 degrees and the right hip to 70 degrees. Internal rotation was limited on the left. Flexion was free on both sides. There



Fig. 14 (case 4).—There is considerable shortening of the extremity associated with a defect in the neck of the femur.

was no atrophy of the left lower extremity. Measurements showed: R.A., 13 inches, L.A., 12½ inches; R.U., 14½ inches; L.U., 13½ inches.

Roentgen examination on November 14 showed slight bowing of the femurs. There were flaring of the lower end of the femoral diaphysis and a defect in the neck of the left femur, with a coxa vara of about 100 degrees. The head of the femur was low in the acetabulum. The acetabulum was relatively normal.

The patient was operated on on November 15. A 2 inch incision was made over the lateral aspect of the left thigh just below the greater trochanter. The subcutaneous tissue was completely incised and retracted. The periosteum was opened immediately below the greater trochanter and completely separated from

the femur. A wedge of bone was taken out of the femur with its base about  $\frac{1}{4}$  inch in width and pointing laterally. The femur was then abducted. After closure of the wound a plaster of paris spica was applied extending from the nipples down to the toes, with the limb in wide abduction.

Examination on Jan. 2, 1930, showed that the wound was healed by primary union. The left hip was in 30 degrees of abduction. It could be brought down to 10 degrees abduction without difficulty. Complete abduction was not limited. The head of the femur rotated with the shaft. No measurements were made because of the abducted position of the extremity.

Roentgen examination of the hips was made after removal of the plaster of paris spica. It showed the coxa vara corrected by a bifurcation operation.



Fig. 15 (case 4).—Appearance after bifurcation operation on the left hip.

The patient was brought back to the hospital because of the return of the limp. Examination on March 11, 1931, revealed that she was in good condition but walked with a limp on the left side. It was noted that there were marked anterior bowing of the shaft of the femur and apparent shortening of the limb. Flexion at the hip joint was possible to a right angle. Extension was complete. Abduction was possible to an angle of about 25 degrees; adduction was free, and extension was completely free. Measurements showed: R.A.,  $16\frac{1}{4}$  inches, and L.A.,  $15\frac{3}{8}$  inches.

The last roentgen picture that was made showed that there was a great distortion of the upper end of the femur, particularly in the subcapital region.

The patient suffered an attack of infantile paralysis during 1931.

Examination on Nov. 23, 1932, showed that the left hip was stable. There was considerable prominence of the greater trochanter. There was no fixed flexion deformity of the hip. It could be flexed to 90 degrees. Abduction on the right

was possible to 45 degrees and on the left to 10 degrees. When the patient stood, the lumbar lordosis was increased. She had a calcaneus deformity on the left. There was just a trace of power in the muscles of the calf. The patient presented a prominent heel. There were good power in the tibialis anticus muscles and slight power in the posticus muscles. There was good power in the peronei. The patient apparently had slight difficulty in the dorsiflexion of the toes. There was good power in the gluteal muscles on both sides. Measurements showed: R.A.,  $19\frac{3}{4}$  inches; L.A.,  $18\frac{5}{8}$  inches; R.T., 13 inches; L.T.,  $11\frac{1}{2}$  inches; R.C., 9 inches, and L.C.,  $7\frac{1}{4}$  inches.

In January 1933 the patient was in the Hospital for Joint Diseases, where a Whitman astragalectomy was performed on the left side.

CASE 5.—S. K., a white girl, aged 5 years, was brought to the Hospital for Joint Diseases on Aug. 24, 1932, because of a limp on the left side, associated with pain. The patient's history and the family history were without significance. The patient began to walk when she was 19 months old and did not limp. Her mother could recall no history of injury, except that the child fell about March of that year. The mother stated that the patient fell down several steps, the injury not being severe. The child remained in bed for a few days. The mother stated definitely that the child did not limp before her injury and had been losing weight since.

Examination on admission showed that the child was in good general condition. She walked with a limp on the left side. The lumbar lordosis had increased slightly. The pelvis was tilted down slightly on the left. The left buttock was flatter than the right. Examination of the spine gave negative results except for slight spasm of the spinal muscles on the right side. The patient had a positive Trendelenburg sign on the left. There was no limitation of motion in the right hip. Abduction was permitted to 70 degrees. Internal and external rotation were free. There was no paralysis of the muscles.

On the left side the greater trochanter was elevated. Flexion at the hip was free. Adduction was free, and internal and external rotation were free. Abduction was permitted to 25 degrees. There was no muscular weakness.

Measurements showed: R.A.,  $21\frac{5}{8}$  inches; L.A.,  $20\frac{1}{2}$  inches; R.U., 24 inches; L.U., 23 inches; R.T.,  $11\frac{5}{8}$  inches; L.T.,  $11\frac{1}{4}$  inches; R.C.,  $8\frac{7}{8}$  inches, and L.C.,  $8\frac{3}{4}$  inches. The length of the right tibia was  $9\frac{1}{2}$  inches. The length of the left tibia was  $9\frac{1}{2}$  inches. The length of the femur from the tip of the trochanter on the right to the lower end of the outer condyle was 12 inches, and on the left from the tip of the trochanter to the lower end of the outer condyle,  $11\frac{3}{8}$  inches. The hips were stable.

Roentgen examination on May 19 showed that the right hip was normal. The left hip showed a coxa vara of 100 degrees. The neck of the femur was shortened. The epiphyseal line was vertical and branched at its inferior portion. There was beginning union of the epiphysis. The head of the femur was low. The acetabulum was practically normal. The neck of the femur was relatively broad.

Operation for removal of a specimen from the head and neck of the left femur and to hasten ossification in the neck of the femur was performed on August 26. The left hip was exposed through a Smith-Peterson incision. The capsule was found to be considerably thickened. There was no excess of fluid in the hip joint. There was no loss of continuity in the neck of the femur or false motion. The appearance of the neck corresponded with the roentgen appearance. A specimen through the superior and anterior portion of the head and neck three-eighths inch in width was removed. This extended from the head of the bone, included about one-half inch of articular cartilage, and passed through the substance of the neck



Fig. 16 (case 5).—There is a *slight* increase in the lumbar lordosis with a tilt to the left.



Fig. 17 (case 5).—Left congenital coxa vara. The neck is short, and bridging of bone is beginning across the defect in the neck of the femur.

and across to the intertrochanteric region, extending slightly downward toward the lesser trochanter. It was perhaps one third of the distance through the diameter of the neck. A culture was made, and the specimen was sent to the laboratory. The bone was dense and hard to cut. A small sliver of bone, which fragmented on removal, was also sent to the laboratory. The main specimen, however, was three-eighths inch in width.

A plaster of paris spica was applied, extending from the upper part of the chest to the toes, with the hip in 25 degrees of abduction, the knee slightly flexed and the foot at a right angle.

For some time after operation a swelling was noted in front of the left hip, but no suppuration ensued.

Culture made at operation gave negative results.

Examination on Jan. 2, 1933, showed that the patient was still wearing a plaster of paris spica and walking about with comfort. When union of the neck is complete, a subtrochanteric wedge osteotomy will be performed for correction of the deformity.

CASE 6.—H. C., a colored boy, aged 8 years, was admitted to the Hospital for Joint Diseases on Jan. 5, 1932. The patient's mother was mentally retarded. The history was unimportant. The birth was normal. The patient was a full-term child. He did not walk until he was 2 years old.

The child was referred to the Hospital for Joint Diseases from the school which he attended because of abnormal posture and a waddling gait. The mother noticed these abnormalities only a short time before admission, although she stated that the patient was in another institution three years before entrance because he complained of being tired and having discomfort in one hip. Traction was applied to the hip. The patient had remained in the hospital for only a few days when his mother removed him.

Examination on admission showed that the patient was in good condition. He presented extreme lumbar lordosis and walked with a waddling gait and a limp on both sides. Trendelenburg's sign was positive on both sides. The greater trochanters were elevated and prominent, being above Nélaton's line. Internal and external rotation were limited on both sides. Bony resistance could be felt on pressure anteriorly below Poupart's ligament on both sides in the position of the femoral artery. Abduction was limited to 15 degrees on both sides. There was a slight flexion contracture of the hips. The patient showed rachitic anterior bowing of the tibias.

The Wassermann reaction was negative.

Measurements showed: R.A.,  $22\frac{1}{4}$  inches; L.A.,  $22\frac{1}{4}$  inches; R.U., 23 inches; L.U., 23 inches; R.T.,  $11\frac{1}{2}$  inches; L.T., 11 inches; R.C.,  $7\frac{1}{4}$  inches, and L.C.,  $7\frac{1}{4}$  inches.

Roentgen examination on admission showed an extreme bilateral coxa vara of 65 degrees. There was a defect in the necks of the femurs with broadened epiphyseal lines, which ran from above and inward, downward and outward. They were branched at their lower borders. The heads of the femurs were low and markedly subluxated. The acetabula were shallow but smooth in outline.

A subtrochanteric wedge osteotomy of the right hip was performed on January 14. An incision about 4 inches in length was made on the lateral aspect of the right thigh, extending from the tip of the trochanter downward on the shaft of the femur. The periosteum was stripped, and a ribbon retractor was introduced. An oblique angular osteotomy was performed, and a wedge was removed from the distal fragment, permitting the hip to be abducted to about 50 degrees without dis-



Fig. 18 (case 6).—Extreme lumbar lordosis.

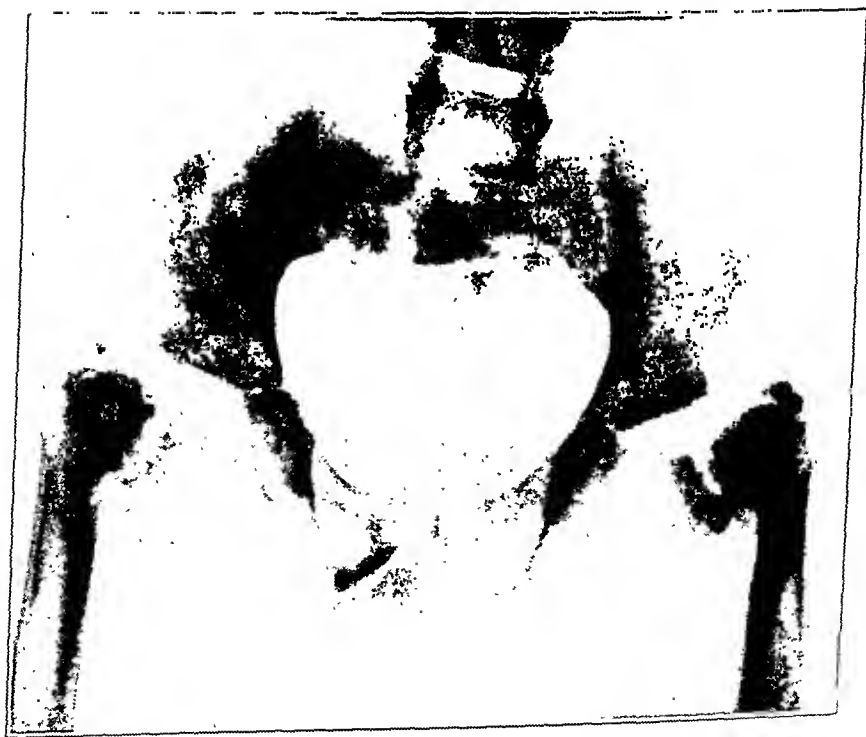


Fig. 19 (case 6).—Typical bilateral congenital coxa vara.

placement of the fragment. A plaster of paris spica was applied, extending from the line of the nipple to the toes.

Drilling of the neck of the left femur was performed on January 28. A 3 inch incision was made over the greater trochanter; the direction of the neck was thereupon palpated by passing a finger around the vastus externus muscle, and three small drill holes were made from below the greater trochanter into the neck. A plaster of paris spica was applied.

Roentgen examination of the two hips on June 3 showed that as a result of the drilling of the neck of the left femur five months before the defect in the neck of this femur had disappeared.



Fig. 20 (case 6).—Appearance six months after operation. There is bony union in the neck of the femur on the left side following operation by drilling. The coxa vara on the right side has been corrected by a subtrochanteric wedge osteotomy. The head of the femur on the right is now higher in the acetabulum.

A wedge osteotomy for the correction of the coxa vara is to be done later. The coxa vara on the right was corrected by operation.

CASE 7.—J. H., a colored boy, aged 10 years, was brought to the Hospital for Joint Diseases in November 1932. The patient's history and the family history were unimportant. The complaint was a limp on the left side. The child had been under the care of a stepmother. Three years before admission she had taken him to another clinic on the advice of the school nurse. The child was not treated. About a year previous to admission the limp was more noticeable. It became steadily more pronounced, but there was no discomfort at any time.



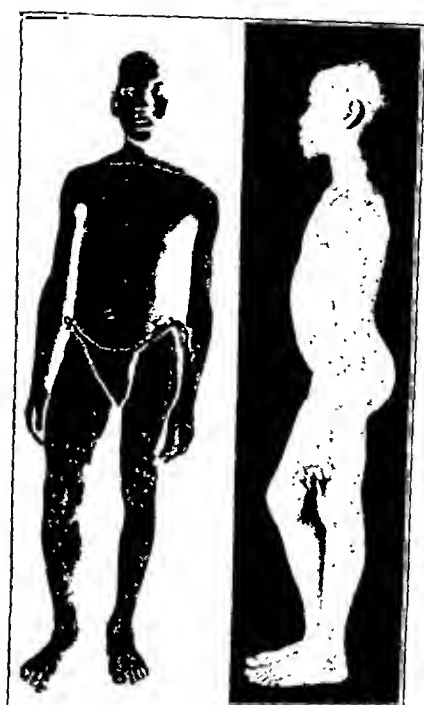


Fig. 21 (case 7).—Shortening of the left lower extremity.



Fig. 22 (case 7).—Congenital coxa vara of the left hip.

Examination on November 4 showed that the patient was in good condition. He walked with a limp on the left side. The greater trochanter on the left was elevated and prominent. There was a positive Trendelenburg sign on this side. Abduction of the left hip was limited at 5 degrees. Adduction was free. Internal rotation was slightly limited. The head of the femur was in the position of the acetabulum. Measurements showed: R.A.,  $26\frac{1}{2}$  inches, and L.A.,  $25\frac{3}{4}$  inches.

Roentgen examination on November 3 showed a coxa vara of 80 degrees on the left. The head of the left femur was large. The neck was attenuated. The epiphyseal line ran from above and inward, downward and outward. It was



Fig. 23 (case 7).—Appearance after a subtrochanteric wedge osteotomy. A drill is inserted into the base of the neck and used as a handle in maintaining the position while the deformity is being corrected.

broadened and branched superiorly. The head of the femur was subluxated downward.

Operation was performed on November 16 on the Albee table, with the limb under traction. The greater trochanter was exposed through a 4 inch incision. A large Steinman nail was driven through the greater trochanter into the neck. A wedge osteotomy with the base laterally, measuring about 1 inch, was then removed from just below the greater trochanter, the apex of the wedge being at the lesser trochanter. It was then found, by gentle abduction, that it was easy to

approximate the two fragments. The wound was closed in this position, and a plaster of paris spica was applied from the nipple line down to the toes on the left side and just above the knee on the right.

Roentgen examination made through the plaster of paris spica on December 1 showed that the coxa vara was corrected by the subtrochanteric wedge osteotomy. There was a drill in the neck of the femur used as a handle at the time of operation.

Examination in January 1933 showed that the patient was still wearing the plaster of paris spica.

The neck of the femur in this patient should be drilled so that the epiphyseal line will become ossified.

CASE 8.—A. J., a white girl, aged 15, was first seen at the Hospital for Joint Diseases in July 1926.



Fig. 24 (case 8).—Bilateral congenital coxa vara. There is complete nonunion of the neck of the femur on the right.

The patient's history and the family history were unimportant. The complaints were bilateral limp and pain in the right hip.

The patient began to walk late; the exact age was unknown. She had limped since she began to walk. For a long time the right hip had pained her after any unusual strain. She had recently made a misstep, and her right foot slipped (she did not fall). The pain in the right hip was acute. Since then the pain had become more marked. After sitting for a while she had great difficulty in starting to walk again.

Examination on July 12 showed that the patient was in good condition. The lumbar lordosis had increased. There was a bilateral limp which was extreme on the right, with instability of the right hip. The greater trochanters were elevated and prominent on both sides, especially on the right. There was apparent shortening of the right lower extremity of about 1 inch. The right hip was flexed to 120 degrees and was in 15 degrees of adduction. The left hip could be abducted to 15 degrees. Flexion was permitted to 90 degrees on both sides. No abduction

was permitted on the right side. The patient had a positive bilateral Trendelenburg sign. Measurements showed: R.A.,  $28\frac{3}{4}$  inches; L.A., 29 inches; R.U.,  $30\frac{1}{2}$  inches; L.U.,  $31\frac{3}{4}$  inches; R.T.,  $16\frac{1}{2}$  inches; L.T., 19 inches; R.C.,  $12\frac{1}{2}$  inches, and L.C.,  $12\frac{7}{8}$  inches.

Roentgen examination showed a bilateral coxa vara of 90 degrees on the left and nonunion on the right, with prominent beaked greater trochanters, an attenuated neck of the femur on the left and an ununited fracture of the neck on the right. Both acetabula were irregular in outline. This was more marked on the right side. The heads were subluxated from the acetabula inferiorly. There was almost complete absorption of the neck of the femur on the right. The acetabula



Fig. 25 (case 8).—Appearance six years after performance of a Whitman reconstruction operation on the right hip.

were shallow. The greater trochanter on the right was displaced upward to a marked degree.

The patient was operated on on July 29, a Whitman reconstruction operation being performed. A large U-shaped incision, with the convexity downward, was made on the lateral aspect of the thigh, and the fascia was cut in the same line. The muscles attached to the greater trochanter were isolated, and the greater trochanter osteotomized and reflected upward. The capsule was then opened, and the head of the femur was removed. There was nonunion of the neck of the femur. The reconstructed neck was placed in the acetabulum. A large portion of the greater trochanter was removed. (This was osteotomized earlier in the operation.) The capsule was closed, and the remaining portion of the trochanter

sutured to the femur lower down. A plaster of paris spica was applied, including the toes, with the hip in 30 degrees of abduction and slight flexion, the knee in slight flexion and the foot at a right angle.

On examination on Nov. 23, 1932, the patient appeared to be in excellent condition. She was somewhat overweight. She walked without assistance but with a marked limp on the right side. The back was flat. There was no evidence of lumbar lordosis. The chest, abdomen, back and upper extremities presented no evidences of deformity.

There was apparently an enormous overdevelopment of the left thigh, due to hypertrophy of the muscles or possibly anterolateral bowing of the femur. Extension at the hip joint was normal. Flexion was possible to an angle of 80 degrees. Abduction was limited to an angle of 5 degrees. Outward rotation was almost

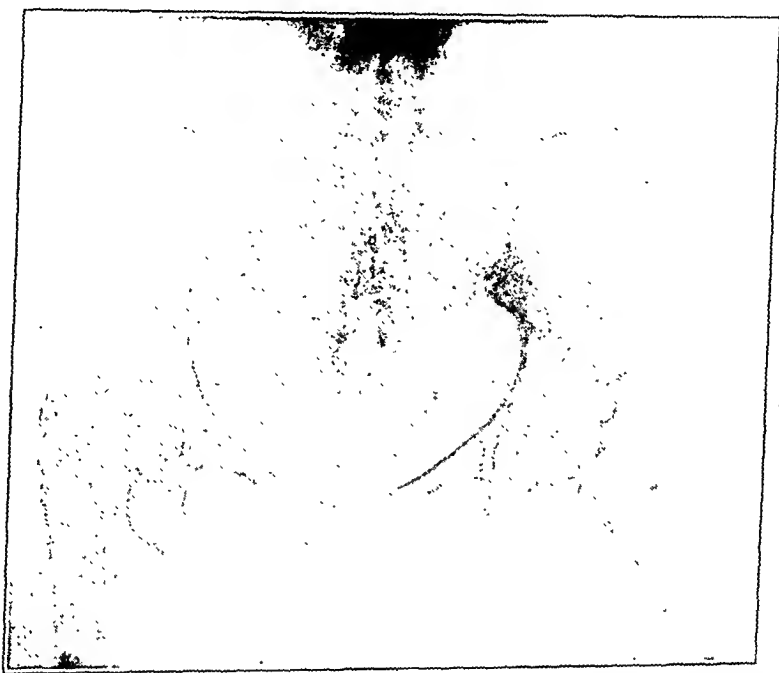


Fig. 26 (case 8).—Appearance six years after a reconstruction operation on the right hip and six weeks after wedge osteotomy on the left hip with removal of the prominent portion of the greater trochanter. Roentgen examination was made between changes of plaster of paris spicas.

free. Inward rotation was markedly restricted. Pressure over the greater trochanter was somewhat uncomfortable. Pressure over the front and back of the hip was not painful. There was a slight degree of hyperextension at the knee joint with a suggestion of knock knee.

There was, similarly, overdevelopment of the right thigh. A U-shaped scar, the result of a reconstruction operation performed six years previously, was seen. Extension at the hip joint was free. Flexion was limited to an angle of 160 degrees. Abduction was possible to an angle of about 10 degrees. Inward rotation was entirely limited. Outward rotation was markedly restricted. There was slight hypertrophy of the knee joint. Manipulation of the limb was not painful. Measurements showed: R.A., 29 inches; L.A., 29½ inches; R.T., 21½ inches; L.T., 23½ inches.

On November 25 a subtrochanteric wedge osteotomy of the left hip was performed, and the prominent portion of the greater trochanter (the superfluous part) was excised.

On Jan. 15, 1933, the patient was still wearing a plaster of paris spica on the left side.

CASE 9.—T. P., a white woman, aged 23. was last examined at the Hospital for Joint diseases on Jan. 20, 1933. The complaints were a limp on both sides and pain in the right hip.

The patient stated that she has three brothers and four sisters, all of whom were taller than she. She said that she did not know at what age she began to



Fig. 27 (case 9).—Bilateral congenital coxa vara with nonunion of the right hip. The distal portion of the neck of the femur has not risen above the acetabulum because of a heavy fibrous union with interlocking of the fragments.

walk, but that she had limped as long as she could remember. Following a fall down a stone stairway three years before, her disability and limp on the right side had increased. She was not completely disabled at this time but remained in bed off and on for a period of two weeks.

Examination on admission showed that when the patient stood the pelvis was level. The right posterior superior iliac spine was half an inch lower than the left. The knees were in contact. There was no lateral inclination of the trunk. The lumbar lordosis was slightly increased. The posture was only fair. There was forward inclination of the head and neck. The patient walked with a limp on both sides and presented a bilateral positive Trendelenburg sign. There was no spasm of the spinal muscles. The spine was flexible. There was slight fullness

to the left in the lumbar region. The greater trochanters were elevated. The plane of the hips, as compared with the shoulders, was apparently normal. The greater trochanter on the right was considerably more elevated than that on the left. The pelvis was rather broadened. The patellas were present. There was no deformity of the feet.

As the patient lay on the table in the supine position, the lumbar lordosis was found to be increased and the right hip flexed to 160 degrees. There was no fixed flexion deformity on the left side. The right hip could be flexed to 90 degrees. The lower extremities were in slight adduction. The right hip could not be abducted. Internal and external rotation of the right hip were about one-third normal. There was sensitiveness to pressure over the anterior aspect of the right hip. The left hip could not be abducted. It could be flexed to 80 degrees. The internal and external rotations were about three-quarters normal. Hyperextension was nearly normal. Measurements showed: R.A.,  $27\frac{1}{4}$  inches; L.A.,  $27\frac{1}{2}$  inches; R.U.,  $30\frac{1}{2}$  inches; L.U., 31 inches; R.T.,  $16\frac{7}{8}$  inches; L.T.,  $17\frac{1}{4}$  inches; R.C.  $11\frac{1}{4}$  inches, and L.C.,  $11\frac{1}{2}$  inches.

Roentgen examination on Nov. 30, 1931, showed a bilateral coxa vara of 80 degrees on the left and 45 degrees on the right. The greater trochanters were beaked and prominent. The neck of the femur on the left was attenuated, but there was bony union. The head of the femur was subluxated inferiorly from the acetabulum. It was much broader than the neck of the femur. The greater trochanter was almost in contact with the side of the pelvis. The acetabulum was small and misshapen.

The right hip showed a lack of union in the neck of the femur. The base of the neck of the femur, however, was in contact with the head fragment by a heavy fibrous union. The head of the femur was almost completely subluxated inferiorly. It was relatively large. The acetabulum was much smaller than that on the left and more irregular in outline. The greater trochanter was in contact with the ilium.

The patient is now considering having an operation on the hips, principally to give her abduction.

CASE 10.—D. R., a white girl, aged 5 years, was admitted to the Hospital for Joint Diseases on Feb. 3, 1933, complaining of pain in the right hip and a right-sided limp.

The family history was unimportant. The patient was a full-term baby. Delivery was normal and noninstrumental. The patient walked at the age of 14 months.

The mother stated that three weeks before admission the child began to walk with a limp on the right side. There was no history of injury or of illness preceding the present condition except mumps one month previously, from which the patient made an uneventful recovery.

Examination on February 4 showed that the child was in good condition. She walked with a limp on the right side. The right hip was more prominent than the left. The right side of the pelvis was held slightly higher than the left. The child presented a positive Trendelenburg sign on the right side.

As the patient lay on the table the greater trochanter on the right was found to be elevated and more prominent than that on the left. The heads of the femurs could be felt in the position of the acetabula. Abduction at the right hip was permitted to 20 degrees; at the left, to 50 degrees. Internal rotation of the right

hip was about two-thirds normal. The right hip was in full extension, and flexion was not limited. Measurements showed: R.A.,  $20\frac{3}{4}$  inches, and L.A.,  $21\frac{1}{4}$  inches.

Roentgen examination on February 3 showed a congenital coxa vara of the right hip of 90 degrees. The epiphyseal line was vertical and branched at its inferior pole. The head of the femur was low in the acetabulum.

The child was operated on on February 6. A lateral incision was made, beginning at the greater trochanter and extending down the shaft. Several drill holes were made through the upper portion of the shaft, extending into the neck of the femur through the epiphyseal line. The deeper tissues were closed with catgut, and the skin with silk; soft dressings were applied.

When the epiphyseal line disappears an operation is to be performed for the correction of the coxa vara.

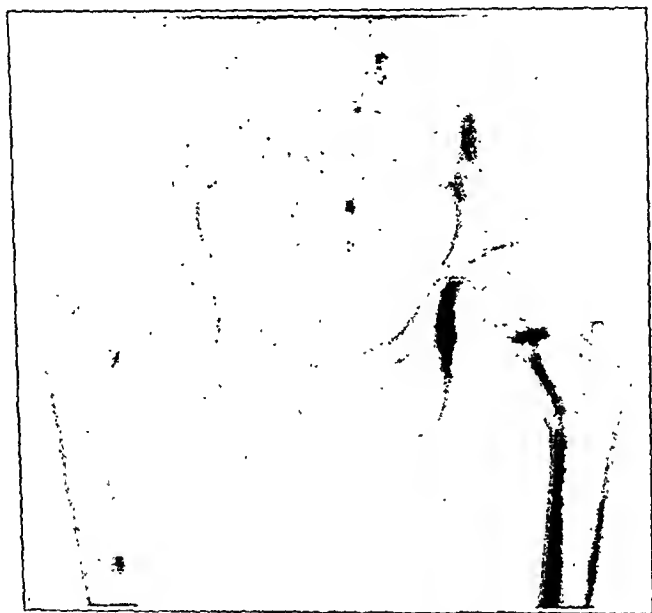


Fig. 28 (case 10).—Right congenital coxa vara.

#### SUMMARY AND CONCLUSIONS

A complete review is here presented of ten cases of congenital coxa vara. Eight of the patients were children, and two were adults. Four of them were males and six were females. Three of the children were colored. The two adults were white. In four of the cases the involvement was bilateral, and in six only one hip was involved. In four of the cases in which the lesion was unilateral the left hip was involved, in two, the right.

A complete review of the history of congenital coxa vara is presented.

The etiology of the condition is not known. The various theories are presented.



The microscopic appearance of the lesion shows nothing characteristic.

The history of the specific case is suggestive of congenital coxa vara, and the case must be differentiated from congenital dislocation, especially if the lesion is bilateral.

The roentgen appearance is unusual and thoroughly pathognomonic. If one is not familiar with the roentgen appearance, the coxa vara will probably be misinterpreted as a fracture of the neck of the femur with nonunion.

The prognosis is governed by the treatment employed.

The conservative treatment (heretofore the only treatment employed) is obsolete. The proper procedure consists of two surgical phases: (1) Bony union should be produced in the defective portion of the neck of the femur, preferably, in my opinion, by drilling, and (2) when this union is secure, the depressed neck of the femur should be elevated by a subtrochanteric wedge osteotomy.

NOTE.—Since this article was written I have seen a number of cases of congenital coxa vara, indicating that the condition occurs more frequently than I previously thought. I have also found it feasible to drill the neck of the femur to cause ossification in the defective portion of the neck and to do a subtrochanteric wedge osteotomy for the correction of the coxa vara at one operation.

Dr. Samuel Kleinberg permitted me to operate on several of these patients. Dr. Leo Mayer, Dr. Harry Finkelstein and Dr. Herman C. Frauenthal allowed me to use material from their services.

#### BIBLIOGRAPHY

- Fiorani, G.: Concerning a Rare Form of Limping, *Gazz. d. osp.* **2**:717 (Aug. 30-Sept. 15) 1881.
- Hofmeister, F.: Coxa Vara: A Typical Form of Curvature of the Femoral Neck, *Beitr. z. klin. Chir.* **12**:245, 1894.
- Kredel, L.: Congenital Coxa Vara, *Centralbl. f. Chir.* **23**:969, 1896.
- Kirmisson, E.: New Facts in the Study of the Rachitic Incurvation of the Femoral Neck (Congenital Coxa Vara), *Rev. d'orthop.* **8**:302, 1897.
- Alsberg, A.: Anatomical and Clinical Considerations of Coxa Vara, *Ztschr. f. orthop. Chir.* **6**:106, 1898.
- Alsberg, A.: Theory and Differential Diagnosis of Coxa Vara, *Ztschr. f. orthop. Chir.* **7**:365, 1899.
- Whitman, R.: Further Observations on Coxa Vara with Particular Reference to Its Aetiology and Treatment, *New York M. J.* **69**:73, 1899.
- Luss, A.: Anatomical Contributions to Coxa Vara, *Inaug. Dissert., Würzburg, Becker's Universitäts Buchdruckerei*, 1899, p. 1.
- Mouchet, A., and Aubion, P.: Congenital Coxa Vara, *Gaz. hebdom. de méd. et de chir.* **4**:481, 1899.
- Bennett, W. E.: Coxa Vara, *Birmingham M. Rev.* **48**:321, 1900.
- Reiner, M.: Relation of Congenital Coxa Vara to Congenital Defect of the Femur, *Ztschr. f. orthop. Chir.* **12**:297, 1903.

- Hoffa, A.: Congenital Coxa Vara, *Deutsche med. Wchnschr.* **31**:1257 (Aug. 10) 1905.
- Feiss, H. O.: Congenital Coxa Vara, *J. A. M. A.* **46**:565 (Feb. 24) 1906.
- Francke: Case Reports on Congenital Coxa Vara, *Ztschr. f. orthop. Chir.* **15**:288 (July) 1906.
- von Kryger, M.: The Etiology of Coxa Vara, *Festschrift, Isidor Rosenthal, Leipzig, Georg Thieme, 1906, pt. 2, p. 257.*
- Helbing, C.: Coxa Vara: An Analysis of the Material from Hoffa's Private Clinic, *Ztschr. f. orthop. Chir.* **15**:502, 1906.
- Ghuilamila, J. D.: Congenital Coxa Vara and Tuberculous Coxitis, *Ztschr. f. orthop. Chir.* **18**:181, 1907.
- Frisch, O.: A Case of Coxa Vara Congenita, *Wien. klin. Wchnschr.* **21**:1558, 1908.
- Rafilsohn, E.: Coxa Vara Congenita, *Inaug. Dissert., Emmendingen, 1908, p. 1.*
- Spitzzy, H.: How Often Is Congenital Coxa Vara Found in Association with a Luxation of the Hip Joint? *Verhandl. d. deutsch. f. Gesellsch. d. orthop. Chir., 1909, p. 19.*
- Drehmann, G.: Contributions to the Etiology and Therapy of Coxa Vara, *Verhandl. d. deutsch. Gesellsch. f. orthop. Chir., 1909, p. 360.*
- Hohmann, G.: Contribution to the Pathology and Therapy of Coxa Vara, *München. med. Wchnschr.* **57**:1219 (June 7) 1910.
- Mayer, E.: Case of Severe Bilateral Congenital Coxa Vara, *Ztschr. f. orthop. Chir.* **25**:323, 1910.
- Drehmann, Gustav: On the Question of Congenital Coxa Vara, *Berl. klin. Wchnschr.* **47**:1752, 1910.
- Mouchet, A., and Segard, M.: Congenital Coxa Vara, *Bull. Soc. anat. de Paris* **87**:114 (March) 1912.
- Mouchet, A., and Segard, M.: Congenital Coxa Vara. *Paris méd.* **1**:421 (March 30) 1912.
- Delitala, F.: Coxa Vara Congenita, *Arch. di ortop.* **30**:382, 1913.
- Schwarz, E.: About Coxa Vara Congenita, *Beitr. z. klin. Chir.* **87**:685, 1913.
- Bley, K.: Coxa Vara, *Inaug. Dissert., Dortmund, Lensing, 1913.*
- Elmslie, R. C.: Coxa Vara, Its Pathology and Treatment, London, Henry Frowde, 1913.
- Perrier: Infantile Coxa Vara, *Rev. d'orthop.* **5**:157, 1914.
- Brand, B.: Coxa vara congenita bilateralis, *Nederl. tijdschr. v. geneesk.* **60**:518 (Feb. 5) 1916.
- Lepoutre: Congenital Coxa Vara, *Bull. et mém. Soc. d. chirurgiens de Paris* **47**:922, 1921.
- Nilsonne, H.: Contribution to the Knowledge of Congenital Coxa Vara, *Acta radiol.* **3**:383 (Nov. 10) 1924.
- Noble, T. P., and Hauser, E. D.: Coxa Vara, *Arch. Surg.* **12**:501 (Feb.) 1926.
- Fairbank, H. A. T.: Unusual Case of Congenital Coxa Vara, *Proc. Roy. Soc. Med.* **20**:237 (Jan.) 1927.
- Peabody, C. W.: Bilateral Defect of Femoral Heads, *J. Bone & Joint Surg.* **9**:288 (April) 1927.
- Fairbank, H. A. T.: Infantile or Cervical Coxa Vara, in Robert Jones' Birthday Volume, New York, Oxford University Press, 1928, p. 225.

- Nilssonne, H.: On Congenital Coxa Vara, *Acta chir. Scandinav.* **64**:217 (Nov. 22) 1928.
- Barr, J. S.: Congenital Coxa Vara, *Arch. Surg.* **18**:1909 (April) 1929.
- Jansen, M.: The Large Brim, the Wide Pelvic Girdle and the Outstanding Number of Hip Anomalies in Man, *J. Bone & Joint Surg.* **11**:461, 1929.
- Kreuz, L.: A Critical Review of the Morphology of Congenital Coxa Vara, *Arch. f. orthop. u. Unfall-Chir.* **28**:106, 1930.
- Bargellini, D.: Evolution of Congenital Coxa Vara, *Arch. ital. di chir.* **27**: 578 (Nov.) 1930.
- Sacerdotte, Gabriele: A Case of "Alternate" Coexistence of Luxation of the Hip and Congenital Coxa Vara, *Minerva med.* **1**:614 (April 21) 1931.

# IRRADIATION IN THE TREATMENT OF TUMORS OF THE PITUITARY GLAND

REPORT OF TWENTY-THREE CASES

CARL W. RAND, M.D.

AND

RAYMOND G. TAYLOR, M.D.

LOS ANGELES

During the past decade increasing interest has been shown in the treatment of tumors of the pituitary gland by high voltage irradiation. Approximately twenty-six years ago, impetus was given to this form of treatment by Gramegna<sup>1</sup> (1909), who was the first to report treatment by this method of a tumor of the pituitary gland. His patient, an acromegalic woman with rapidly failing vision, was given two courses of treatment in the years 1907 and 1908, respectively. The first was followed by some improvement in her vision, which later failed. She was not helped by the second course of treatment. He felt that the acromegalic features of the case were arrested. The radiation was given through the mouth, as being the nearest portal of entry to the pituitary gland and offering relatively little bony resistance to the rays. He felt that the mucous membranes tolerated irradiation as well as, or better, than the skin, and that the brain and other normal tissues of the central nervous system, such as the optic nerves, were not injured by the treatment.

Greater attention has been paid to irradiation of chiasmal lesions in Europe than in this country. Magnus<sup>2</sup> (1928), Nordentoft<sup>3</sup> (1928), Bécélère<sup>4</sup> (1922 and 1929), Sgalitzer<sup>5</sup> (1929), Fraticelli<sup>6</sup> (1930),

---

1. Gramegna, A.: Un cas d'acromégalie traité par la radiothérapie, *Rev. neurol.* **17**:15, 1909.

2. Magnus, Hans: Röntgenbestrahlungen der Hypophysentumoren, nebst Bemerkungen über hemianopische Pupillenstarre, *Arch. f. Ophth.* **121**:225 (Oct. 13) 1928.

3. Nordentoft, Jacob: Bons effets de la radiothérapie dans un cas de tumeur hypophysaire, *J. radiol. et d'électrol.* **12**:280 (June) 1928.

4. Bécélère, M. A.: Technique, résultats, indications et contre indications de la roentgentherapie des tumeurs hypophysaires, *Rev. neurol.* **38**:808, 1922; Les adénomes hypophysaires de l'adolescence et de l'enfance justiciables de la radiothérapie, *ibid.* **1**:463, 1929.

5. Sgalitzer, Max.: Erfahrungen mit der Röntgenbehandlung bei Hypophysengeschwülsten, *Wien. med. Wchnschr.* **79**:566, 1929.

6. Fraticelli, Aureliano: La roentgenterapia nei tumori ipofisari a sindrome chiasmatica: tecnica e risultati, *Atti di ottal. e ocul.* **58**:756, 1930.

Jusefowa, Czerny and Heinismann<sup>7</sup> (1930) and Nemenow and Jugenburg<sup>8</sup> (1928) have reported series of cases in which this treatment was given. The consensus seems to be that temporary improvement of visual disorders resulting from the pressure of a tumor of the pituitary gland on the optic chiasm follows high voltage treatment. One of Nemenow's patients retained practically normal vision for seven years following treatment. Bécélère expressed the belief that irradiation does not completely stop the evolution of the adenoma, but felt that it should be tried before resorting to surgical intervention. Jusefowa, Czerny and Heinismann advised decompression prior to irradiation in cases showing increased intracranial pressure. Most observers are in agreement that acromegalic symptoms in general have been arrested by high voltage treatment.

In this country less attention has been paid to irradiation of tumors of the pituitary gland, more emphasis having been placed on their surgical treatment. Frazier and Grant<sup>9</sup> (1925), in reviewing one hundred cases of pituitary lesions, stated that there were only three in which unquestionably the lesions were favorably affected by irradiation, and they doubted the permanency of these results. They did not state how many patients of the series received high voltage irradiation. Later, in 1930, Frazier,<sup>10</sup> in a report of a larger series of pituitary disorders, two hundred and thirty-one cases, again discussed the question of irradiation. Ten cases were reported in detail, in two of which the patients received high voltage irradiation. One received three courses, with marked improvement for more than three years. He stated: "This is the only case in my experience in which the beneficial effects of irradiation have been sustained." The second patient was not helped by one series, and was subsequently improved by transfrontal craniotomy. Frazier asked: "Under what circumstances is one warranted in trying the effects of irradiation, with the risk of what delay in operation may mean?" He based his answer, not so much on the distortions of the field as on the appearance of the disk. He felt that if the capillarity of the disk is essentially normal operation can be postponed with propriety, but that, as is frequently the case when the

7. Jusefowa, F. L.; Czerny, L. I., and Heinismann, I.: Roentgen Therapy in Tumors of the Area of the Hypophysis, *Klin. Monatsbl. f. Augenh.* **85**:344 (Sept.) 1930.

8. Nemenow, M., and Jugenburg, Anna: Die Strahlenbehandlung der Hypophysentumoren, *Strahlentherapie* **30**:238, 1928.

9. Frazier, C. H., and Grant, F. C.: Pituitary Disorder: A Digest of One Hundred Cases with Remarks on the Surgical Treatment, *J. A. M. A.* **85**:1103 (Oct. 10) 1925.

10. Frazier, C. H.: A Series of Pituitary Pictures; Commentaries on the Pathologic, Clinical and Therapeutic Aspects, *Arch. Neurol. & Psychiat.* **23**:656 (April) 1930.

patient is already blind in one eye and vision is rapidly failing in the other, procrastination is never justifiable. He emphasized the fact that irradiation will have no influence on a pituitary lesion which is already cystic, and added that there is no way, except by operation, of determining the precise nature of the lesion. Towne<sup>11</sup> (1926 and 1930) reported a series of five cases of tumor of the pituitary gland treated by roentgenotherapy. Two cases reported in 1926 were again reviewed in his 1930 report. In general, he summarized the situation as follows: "Eighty per cent of pituitary adenomas are solid, and twenty per cent are cystic. Twenty per cent of patients retain useful vision for more than five years after operation; eighty per cent show no improvement or, after more or less marked improvement, have recurrences after about two years. Operative treatment of pituitary adenomas has a mortality ranging from 7 per cent upward; roentgen-ray treatment has no mortality." Cases were reported showing long-standing favorable results from roentgen treatment and likewise showing that if irradiation does not give good results, a diagnosis of cystic tumor, favorable for operation, may be made. He felt that all pituitary adenomas should be treated by roentgen rays under the observation of an ophthalmologist and a neurosurgeon, and that surgical intervention should be undertaken short of six months only when visual acuity and the fields recede under roentgen treatment. Dyke and Gross<sup>12</sup> in 1931, discussed roentgenotherapy of tumors of the pituitary gland, and reported five cases in which it was given. They stated that for some years it has been Elsberg's opinion that every patient with defects of the visual fields due to a pituitary neoplasm should first receive a course of high voltage therapy. This should be continued if improvement occurs. If, on the other hand, the visual fields and acuity recede, surgical intervention is indicated. Like Towne, they looked on irradiation as a diagnostic test to separate the patients requiring surgical intervention from those not immediately requiring it. Three of their patients, presumably having adenomas, showed definite improvement in both visual fields and visual acuity. The headache was entirely relieved. The two remaining patients showed no further loss of vision, although they were said to have improved subjectively. Dyke and Gross mentioned an additional case, in which the patient had been treated elsewhere with only temporary improvement. At operation later the lesion proved to be a cystic adenoma. One patient of their series, with acromegaly and

11. Towne, E. B.: Roentgen-Ray Treatment of Pituitary Tumors, *Arch. Neurol. & Psychiat.* **15**:92 (Jan.) 1926; Treatment of Pituitary Tumors: The Role of the Roentgen Ray and of Surgery Therein, *Ann. Surg.* **91**:29 (Jan.) 1930.

12. Dyke, Cornelius G., and Gross, Sidney W.: The Roentgenotherapy of Pituitary Tumors, *Bull. Neurol. Inst. New York* **1**:211 (June) 1931.

presumably a chromophil adenoma, was improved. Heuer,<sup>13</sup> in 1931, gave an excellent résumé of the surgical treatment of tumors and other lesions about the optic chiasm. His closing words concerning irradiation of the lesions summarize his attitude. He stated:

The X-ray has been a distinct contribution to the treatment of hypophyseal adenomata, both chromophil and chromophobe. In certain cases it may check the growth of the tumor and delay or make unnecessary its operative partial removal. It is a valuable adjunct and should in our opinion be used routinely in the post-operative treatment of these tumors. It is possible that the improvement in the results of the operative treatment of hypophyseal adenomata, attributed in part by us to the more logical removal of that portion of the tumor directly compressing the chiasm and nerves, may in greater part be due to more frequent use of post-operative X-ray treatments. The use of this method is not without danger. Its use as an alternative to surgery presupposes accurate pathological diagnosis, for, so far as our present knowledge goes, the hypophyseal adenomata alone of the many lesions about the chiasm respond to it. Its indiscriminate use in lesions about the chiasm may do great harm; and it should in our opinion be given only with the knowledge and consent of those familiar with these lesions.

Sachs<sup>14</sup> (1931), in discussing the treatment of tumors of the pituitary gland, favored surgical intervention, although in discussing two cases of chromophil adenoma in which operation was done with beneficial results, he expressed the opinion that both cases could have been equally well arrested with high voltage therapy. He added: "Certainly, in the light of our present knowledge, one should try this first, before resorting to operation." Cushing<sup>15</sup> (1932) was anything but enthusiastic regarding irradiation of the lesions. He stated:

So far as concerns radiotherapeusis, at least in the case of the chromophobe adenomas, it is safe to say that it will come to be discarded just as radiation for exophthalmic goitre has been, so soon as neurosurgeons as a class perfect themselves in the details of the operative procedure. It may reasonably be assumed that in those clinics where radiation for these lesions is still routinely advocated, the surgical results have been poor and the mortality disturbingly high.

He added in a footnote: "The chromophile adenomas in our experience appear to be more definitely susceptible to radiation."

Homans<sup>16</sup> (1932) was somewhat more enthusiastic regarding irradiation of both chromophobe and chromophil adenomas. He stated: "In both forms of adenoma, radio-therapy is beneficial and may deserve

13. Heuer, George J.: *The Surgical Approach and the Treatment of Tumors and Other Lesions About the Optic Chiasm*, Surg., Gynec. & Obst. **53**:489 (Oct.) 1931.

14. Sachs, Ernest: *Diagnosis and Treatment of Brain Tumors*, St. Louis, C. V. Mosby Company, 1931, p. 296.

15. Cushing, Harvey: *Intracranial Tumours*, Springfield, Ill., Charles C. Thomas, Publisher, 1932, p. 79.

16. Homans, John: *A Textbook of Surgery*, Springfield, Ill., Charles C. Thomas, Publisher, 1932, p. 564.

a trial before recourse is had to surgery. The chromophile adenomas appear to be particularly susceptible to the effects of radiation." Bailey<sup>17</sup> (1933) stressed the point that effective treatment of pituitary adenomas can be controlled only by carefully examining the visual fields. He was not adverse to, and even recommended, high voltage therapy in such cases, provided the vision is not jeopardized. He stated:

The growth of an adenoma can sometimes be retarded and even a regression in size obtained by persistent roentgen-radiation. This observation has been often repeated and certainly, if there is no immediate danger to vision, roentgen-radiation should be tried in every case. It should not be forgotten, however, that serious accidents may occur, noticeably from edema or from hemorrhage into the tumor immediately after too energetic radiation. In either case vision rapidly fails and prompt operation is necessary.

Globus<sup>18</sup> (1933) considered that surgical intervention in adenoma of the pituitary gland yielded the most satisfactory results. Regarding high voltage therapy, he stated:

Occasionally high voltage roentgen or radium therapy may give rise to apparent improvement and to the false hope that the pathologic process has been arrested. However, in the course of time an explosive reappearance of symptoms will shatter one's belief that the disease process may remain permanently dormant. Unfortunately, at such a time the expanded lesion has extended into such regions as to make a surgical approach prohibitive.

He cited the case of a woman, aged 31, who had unmistakable signs of tumor of the pituitary gland which showed its presence by amenorrhea for sixteen years. At the age of 26 the diagnosis of tumor of the pituitary gland was made. A bitemporal hemianopia existed at that time. After an unsuccessful attempt to remove the growth by an intranasal approach, radiotherapy was instituted, with gratifying improvement and widening of the visual fields. This improvement was maintained for five years. Following this the patient showed signs of intracranial extension of the growth, and apparently died during a craniotomy for removal of the growth. He commented that removal of the tumor at an earlier stage might have altered the sequence of events. The autopsy showed a relatively small tumor of the pituitary gland, with a large extension in the interpeduncular space and invasion of the third ventricle. He did not state the type of tumor. One wonders whether, after having five years of relief from radiotherapy, her life might not have been prolonged and improvement might have occurred again if further radiotherapy, instead of surgery, had been adopted.

17. Bailey, Percival: *Intracranial Tumors*, Springfield, Ill., Charles C. Thomas, Publisher, 1933, p. 111.

18. Globus, J. H.: *Tumors Affecting the Optic Chiasm and Optic Tracts: A Brief Critical Survey of Their Clinical and Anatomic Features*, Arch. Ophth. 9:729 (May) 1933.



The use of high voltage therapy was concretely brought to the attention of one of us (C. W. R.) in 1920, when a patient having a symptomatic chromophobe adenoma was given irradiation by Dr. Albert Soiland of Los Angeles. The patient, a man, had a temporal hemianopia on the right, and a loss of vision in the lower fields on the left, general hypopituitary symptoms, and a greatly enlarged sella turcica with atrophy of the posterior clinoidal processes. Primary optic atrophy was present on both sides. The treatments were given through four portals of entry, cross-firing the hypophysis. The exact dosage cannot be computed in the terms of units now employed, but he is said to have received doses from a high potential source. His vision soon began to improve, and his headaches disappeared. Subsequently, high voltage treatments were given him in Stockholm. Ten years later he was reported as being free from headaches, having serviceable vision and being clinically well. The case is not included in this series, as the details were not sufficiently followed to permit its use as an accurate clinical record. However, there is little doubt that the patient was greatly benefited by high voltage radiation, and that the period of improvement has lasted for more than a decade.

#### REPORT OF CASES

CASE 1.—*Advanced pituitary tumor with acromegaly, probable chromophil adenoma (unverified). Blind in the right eye; temporal hemianopia in left visual field; headaches. Marked improvement in left visual field nine years after one course of high voltage irradiation.*

E. G., a woman, aged 54, married, a housewife, was referred by Dr. A. P. Maisch, Los Angeles, on June 11, 1924. Failing vision had been noticed since 1919. During 1919 there was a period of terrific headaches associated with nausea and vomiting and accompanied by two convulsions. Later the headaches became less severe; marked mental changes in the nature of *Witzelsucht* and considerable weakness of the left leg developed.

Examination revealed an acromegalic woman about 5 feet, 3 inches (160 cm.) tall, weighing 145 pounds (65.8 Kg.). The hands were thick and spadelike, the feet large and the features coarsened, with an increased growth of hair on the face. She was completely blind in the right eye, and ocular movements on this side were limited. The right pupil was dilated and did not react to direct light, but reacted consensually. The left pupil was smaller and reacted to direct light, but not to consensual light. There was advanced primary optic atrophy on both sides, the disks being sharply outlined and very pale. The veins were large, but the arteries were almost threadlike. The deep reflexes were increased on the left side. No abnormal reflexes of the Babinski group were present. The Wassermann reaction of the blood was negative. Roentgenograms of the skull showed marked enlargement of the sella turcica and rarefaction and thinning of the floor of the posterior clinoid processes (fig. 1).

Operation was advised, but refused. Because of the refusal and the fact that the patient was fast becoming blind, a course of high voltage therapy was given. This was followed by a violent reaction, accompanied by headaches and hyperthermia. She remained in a semicoma for twenty-four hours, and exhibited signs

of increased intracranial pressure for two days subsequently. Figure 1 shows the visual fields on June 27, shortly before irradiation. It also shows the visual fields on Oct. 30, 1931, more than seven years later. On the left side, there is some improvement both in the fields and in acuity. We have recently been informed (June 4, 1933) that she is free from headaches and is mentally clearer, but has an occasional convulsion. On the whole, nine years after high voltage therapy, her general condition is better, and she has serviceable vision in her left eye.

*Comment.*—This patient was the first treated. She received only a moderate total dose of irradiation, but a larger initial dose than we were

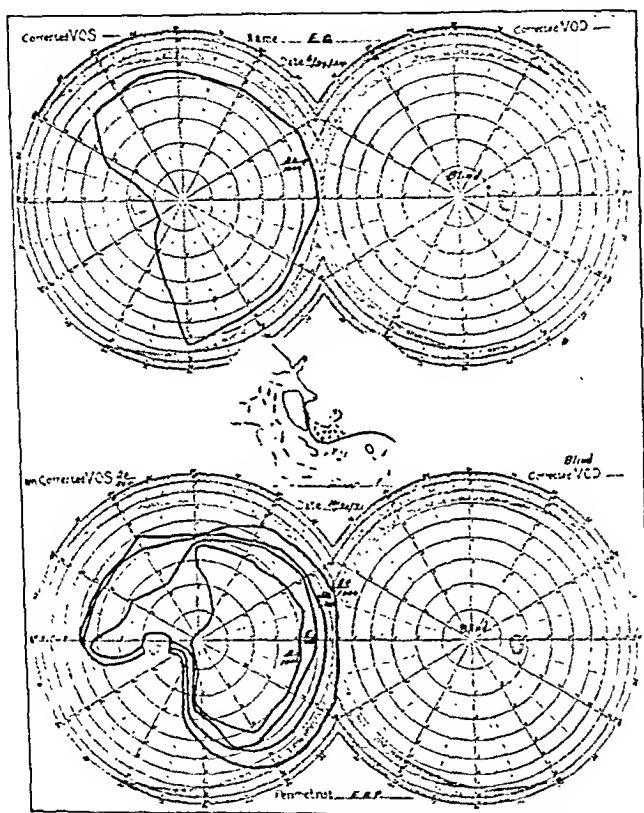


Fig. 1 (case 1).—Chromophil adenoma (unverified). The perimetric fields before irradiation are shown above, and those following irradiation below. While there was no return of vision in the blind right eye, vision was improved in the left for more than seven years. Operation was refused. The insert shows a tracing of the enlarged sella turcica. The posterior clinoid processes are practically obliterated.

in the habit of giving subsequently. She received approximately 300 roentgens (r) in two successive days, and a week later approximately 400 r at one treatment. She had the most violent reaction, following the last treatment, of any patient of the series, consisting of nausea, vomiting and convulsions; in fact, she had the only reaction that was alarming. Prior to treatment she showed signs of increased intracranial

# Summary of Cases

Comment

Case	Sex	Age	Duration of Visual Disturbances and Hypophysical Symptoms	Type of Tumor	High Voltage Therapy	Operative Procedure	Comment
1	F	54	5 yrs.; in right eye, complete blindness; in left, atypical temporal hemianopia; headaches; acromegaly	Chromophil adenoma (unverified)	3 single doses in 10 days	Operation refused	No improvement in right eye (blind); improvement in left eye lasting 9 yrs.; no advance in acromegaly; headaches relieved
2	M	23	3 yrs.; in right eye, temporal hemianopia; left eye blind; hypopituitarism	Chromophobe adenoma (grossly verified)	2 series—second one short	Exploration of pituitary region; partial removal of mulberry-like tumor, followed by high voltage therapy	No improvement of vision following preoperative irradiation; improving operation in right eye for 1 yr. following operation; ultimate blindness; death 2 yrs. later; autopsy refused
3	M	42	Falling vision in right eye 2 mos.; in left, 10 yrs.; bitemporal hemianopia; headaches; hypopituitarism	Chromophobe adenoma (unverified)	3 series—second short	None	Definite improvement of visual fields and acuity for more than 6 yrs.; headaches relieved
4	F	50	Falling vision in right eye 3 yrs., going on to practical blindness; in left eye vision remaining only in upper nasal quadrant	Adenocarcinoma (verified)	1 series, irregular	Exploration of pituitary region; partial removal of adenocarcinoma	No improvement of vision following irradiation; death following operation; autopsy refused
5	M	49	3½ yrs.; atypical bitemporal hemianopia	Adenocarcinoma (verified)	5 series, followed by radium therapy	Exploration; adenocarcinoma of the pituitary gland found; partial removal	Slight improvement of fields following early irradiation which soon ceased; vision worse 15 mos. later
6	M	16	1 yr. bitemporal hemianopia; headaches; hypopituitarism	Chromophobe adenoma (unverified)	2 series—second short	None	Improvement in vision for more than 3 yrs.; headaches relieved; grew to 6 feet and gained 16 pounds
7	F	32	9 mos. bitemporal hemianopia, marked, contraction of fields; amenorrhea, 2 yrs.	Chromophobe adenoma (unverified)	2 series preoperatively	Exploration of pituitary region; partial removal of chromophobe adenoma	Improvement of visual fields for more than 3 yrs.; amenorrhea persisted
8	F	45	5 mos.; island of vision in right lower nasal quadrant; left temporal hemianopia; headaches	Chromophobe adenoma (verified)	1 series	Operation refused	Vision in right eye stationary after 2 yrs.; vision in left eye improved after 2 yrs.; headaches relieved
9	M	39	2 yrs.; right eye, falling vision; bitemporal hemianopia when seen	Cystic chromophobe adenoma (unverified)	Yes*	Operation refused	Continued failure of vision; should have exploration
10	M	40	4 yrs.; atypical bitemporal hemianopia; diabetes insipidus; headaches; hypopituitarism	Chromophobe adenoma (unverified)	Yes*	Operation refused	Temporary improvement; should have exploration
11	F	41	3½ yrs.; falling vision; right eye almost blind; left eye, temporal hemianopia	Chromophobe adenoma (unverified)	Yes*	Operation refused	Slight improvement in left eye for more than 4 yrs.; little improvement in right eye

					Yes*	Cystic chromophobe adenoma (verified)	Temporary improvement of vision following irradiation and surgery, now failing; duration of improvement, 2 yrs.; marked gain in weight following operation
12	F	41	7 mos.; failing vision; bitemporal hemianopia; greatest visual disturbance in left eye; headaches			Cystic chromophobe adenoma (verified)	Return of visual fields to normal; no improvement in headaches; acromegalic features unchanged
13	F	30	Visual disturbance slight; acromegaly advanced; severe headaches, 6 yrs.	2 series, 2 years apart		Chromophil adenoma (unverified)	Operation
14	M	63	18 mos.; bitemporal hemianopia; greatest disturbance on right	1 series		Chromophobe adenoma (verified)	None
15	M	17	10 yrs.; failing vision; advanced bitemporal hemianopia; mild hypopituitarism	2 series		Chromophobe adenoma (unverified)	Definite improvement in fields maintained for more than 3 yrs.
16	M	42	5 yrs.; advanced bitemporal hemianopia; severe headaches	2 series*		Chromophobe adenoma (unverified)	Definite improvement in fields maintained for more than 2 yrs.; complete relief from headaches
17	M	39	1 yr.; failing vision; atypical bitemporal hemianopia; hypopituitarism	2 short series		Chromophobe adenoma (unverified)	Moderate improvement of fields continued for 18 mos.
18	M	44	4 yrs.; right eye, small island of vision in upper nasal quadrant; left eye, practically complete blindness; severe headache; Wassermann ++-++-; acromegaly	3 series post-operatively		Chromophil adenoma (unverified)	Parent's vision in both eyes returned practically to normal and maintained 2 yrs.; headaches relieved
19	M	49	5 yrs.; failing vision; atypical hemianopia, most marked in left eye; headaches	1 series		Chromophobe adenoma (unverified)	Further failure of vision in left eye; definite improvement of vision in right eye maintained more than a year; should have exploration
20	M	52	6 yrs.; failing vision in right eye; later, almost blind; bitemporal hemianopia in left eye	1 series		Chromophobe adenoma (grossly verified)	No improvement during observation; sudden death following an explosion; coroner reported, "glomatomous tumor occupying sella turcica;" undoubtedly adenoma; specimen unavailable for study
21	F	30	2 mos.; atypical bitemporal hemianopia; headaches; hypopituitarism; amenorrhea 9 yrs.	1 series		Cystic chromophobe adenoma (verified)	No improvement of fields following irradiation; return of fields to normal within 2 wks. after operation
22	F	27	1 yr.; atypical bitemporal hemianopia; headaches; mild acromegaly	1 series		Chromophil adenoma (unverified)	Marked improvement of fields 5 mos. after irradiation
23	F	40	3 wks.; atypical hemianopia; acromegaly 3 yrs.; diabetes 6 wks.; headaches; abducens palsy on right	1 series		Chromophil adenoma (unverified)	Return of fields to normal 3 mos. after irradiation; disappearance of abducens palsy on right; headaches markedly decreased

\* Treated elsewhere, details not known.

pressure, and possibly the intense reaction was due to further increase of pressure from postirradiation congestion in the tumor. This made us cautious in the amount of radiation administered in subsequent cases. In most, if there was a temporary increase in the headaches or increased blurring of vision, we either decreased the dose or lengthened the intervals between treatments.

CASE 2.—*Pituitary tumor; probable chromophobe adenoma (grossly verified). Hypopituitarism. Incomplete operative removal, followed by high voltage irradiation.*

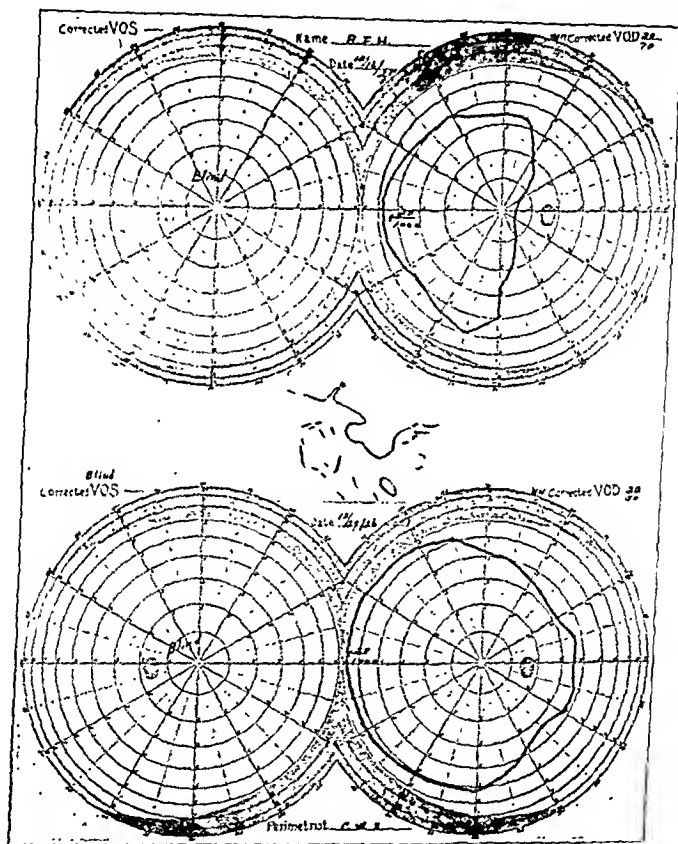


Fig. 2 (case 2).—Chromophobe adenoma (grossly verified). Above are the perimetric fields before irradiation or operation, and below are the fields one year subsequent to partial removal of the tumor followed by a course of high voltage therapy. The insert shows a much enlarged sella turcica invading the sphenoid sinuses, and the absence of posterior clinoid processes.

tion. Total blindness in left eye, uninfluenced. Vision in right eye temporarily improved, but later lost.

B. F. H., a man, aged 23, single, a tutor, was referred by Dr. F. B. Clarke, Long Beach, Calif., on Dec. 14, 1925. There had been failing vision in the left eye for three years and in the right eye for the preceding few months. At the time of our first examination, the patient was totally blind on the left side, with a temporal hemianopia on the right (fig. 2). There had been a period of severe headaches

three years previously. At the time of examination, headaches were infrequent and mild.

Examination revealed a man, 5 feet, 7 inches (170.1 cm.) tall, weighing 190 pounds (86.2 Kg.), obese, of feminine build and showing characteristics of hypopituitary disturbance. The right disk was choked, and the left showed hazy margins, the disk itself being distinctly pale. The latter appeared to be a secondary atrophy following an old choked disk. There was palsy of the external rectus muscle on the left. The right pupil did not react to direct light; the left reacted sluggishly. The Wassermann reaction of the blood was negative. Roentgenograms of the skull on December 16 showed erosion of the posterior clinoid processes; the floor of the sella turcica was practically gone, and there was marked enlargement of the region of the sella turcica (fig. 2).

On Dec. 6, 1925, and Jan. 2, 1926, a two stage operation was performed, and a left frontal approach of the pituitary gland was carried out. An oval, mulberry-like tumor was found, which was highly vascular, and was only partially removed. Four and a half months following the operation he was given fairly vigorous high voltage therapy, with some improvement in vision on the right for approximately twelve months (fig. 2). He died on March 19, 1927, and at that time had only perception of light in the right eye. Permission for autopsy was not obtained.

*Comment.*—The tumor in this case was partially removed at operation, and decompression was carried out five and a half months prior to high voltage therapy. The treatment was given fairly rapidly without untoward reaction. In spite of both methods of treatment and temporary improvement, the patient's vision completely failed, and death occurred approximately two years after the patient came under observation.

*CASE 3.—Pituitary tumor; probable chromophobe adenoma (unverified). Bitemporal hemianopia; headaches; hypopituitarism. Improvement maintained for more than six years following high voltage irradiation.*

H. J. F., a man, aged 42, married, a rancher, was referred by Dr. George W. McCoy, Los Angeles, on Sept. 7, 1926. There had been failing vision in the left eye for the previous ten years. About two months before coming under our observation vision in the right eye began to fail. At our first examination the visual fields showed a fairly typical bitemporal hemianopia (fig. 3). During this time he had been having rather severe frontal and bitemporal headaches. These headaches were intermittent, usually lasting from one to two days at a time. He tired easily.

Examination revealed a man 5 feet, 7 inches tall, weighing 150 pounds (68 Kg.). His skin was rather dry and the beard was not as heavy as formerly, both moderate characteristics of hypopituitary disturbance. The eyegrounds showed both disks sharply outlined, with clear optic cups and moderate temporal pallor. The left disk was paler than the right. The Wassermann reaction of the blood was negative. The neurologic examination revealed no abnormality. Roentgenograms of the skull showed a complete loss of the posterior clinoid processes, with considerable absorption of the anterior processes. The sella turcica was enlarged and the floor depressed (fig. 3).

*Comment.*—The patient was given high voltage treatment, with definite improvement of the visual fields which has lasted over six years (fig. 3). He received three moderate courses of high voltage irradiation

without much reaction. The first was unsatisfactory from a roentgenologic point of view, because of small doses, 150 r three times a week for three weeks; the other two, because of irregularity in the time of treatments. However, clinically the patient was benefited for more than six years.

CASE 4.—*Adenocarcinoma of the pituitary gland (verified). No improvement following high voltage therapy. Death following operation.*

G. F. R., a woman, aged 50, married, a housewife, was referred by Dr. C. B. Walker, Los Angeles, on Oct. 19, 1928. For about eight years she had been

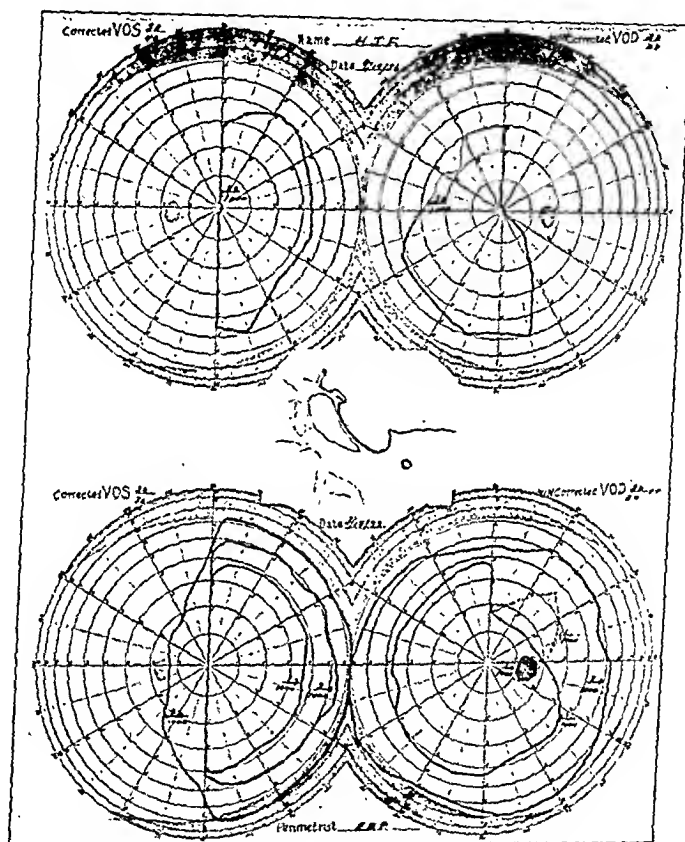


Fig. 3 (case 3).—Chromophobe adenoma (unverified). In the upper fields the fairly typical bitemporal hemianopia which existed before high voltage therapy (1926) is seen, while the fields below show the marked improvement following one course of high voltage irradiation. The improvement lasted for more than six years. The insert shows a tracing of the sellar region. The sella turcica is of the large, flattened type, with the posterior clinoid processes practically absent and little invasion of the sphenoid sinuses.

subject to sick headaches, which, during the preceding three years, had decreased. Since then she had failing vision, which went on to almost complete blindness in the right eye and low vision in the left (fig. 4).

Examination revealed an undersized, undernourished woman, with few, if any, general characteristics of pituitary disorder. There was double primary optic atrophy, with marked contraction of the vessels. The left pupil was larger than the

right, and both were practically static to light. The Wassermann reaction of the blood was negative. Roentgenograms of the skull showed enlargement of the sella turcica, with marked thinning of the floor and complete absorption of the posterior clinoid processes (fig. 4).

She was given a course of high voltage therapy consisting of twelve doses of 200 r given at irregular intervals during a period of four weeks. In spite of this her vision continued to fail, and irradiation was stopped on November 25. By Feb. 7, 1929, she was completely blind in the right eye (fig. 4). She was operated on in February, at which time a mulberry-like hypophyseal tumor was found. Small portions were nibbled away. Microscopic examination revealed evidence of

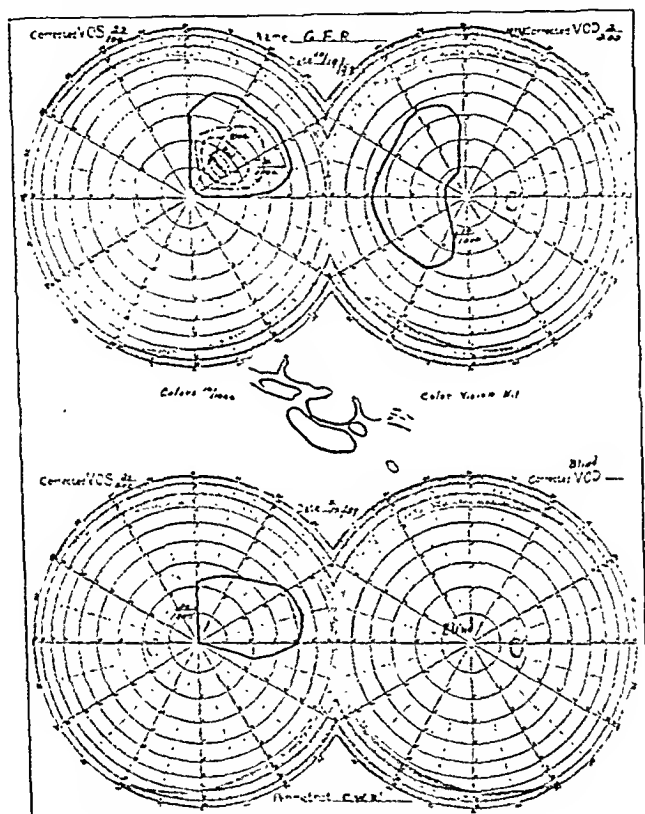


Fig. 4 (case 4).—Adenocarcinoma (verified). Above are the perimetric fields before irradiation, showing temporal hemianopia on the right and the remaining field of vision in the upper nasal quadrant on the left. Below, the fields show the loss of vision following roentgen irradiation four months later. The insert shows a moderately enlarged sella turcica with little destruction of the anterior or posterior clinoid processes and little encroachment on the sphenoid sinuses.

adenocarcinoma of the pituitary gland. Following the operation cerebral edema developed, and the patient died twelve hours later.

*Comment.*—This patient had treatment over a period of five weeks, which, from a roentgenologic point of view, was unsatisfactory because the treatments were given at irregular intervals. No favorable reaction followed the irradiation. Autopsy was not permitted.



CASE 5.—*Pituitary tumor, adenocarcinoma (verified). Temporary improvement following high voltage therapy and operation.*

H. G. E., a man, aged 49, married, a banker, was referred by Dr. H. Douglas Eaton, Los Angeles, on Sept. 13, 1929. The patient first noticed failing vision three and a half years previously, and for about three years had had considerable headache, especially on waking in the morning. During the previous year there had been little if any headache. The visual fields, when first seen, showed an atypical bitemporal hemianopia (fig. 5).

Examination revealed a man 5 feet, 7 inches tall, weighing 126 pounds (57.2 Kg.). He had a pasty look and was of the hypopituitary type, with dry

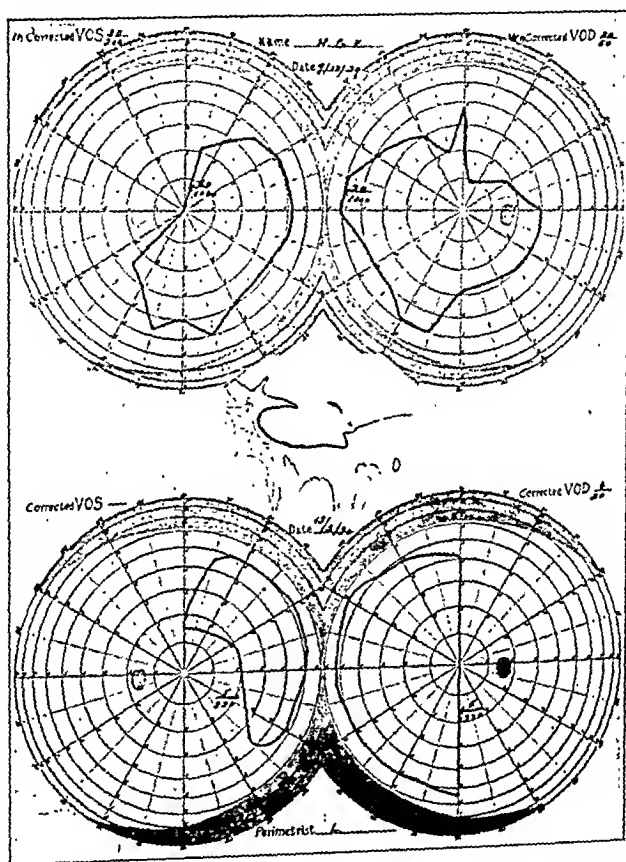


Fig. 5 (case 5).—Adenocarcinoma (verified). Above are the visual fields before irradiation or surgical intervention, and below, the fields fifteen months later following an exploratory operation. The insert shows the enormously enlarged sella turcica, the posterior clinoid processes practically obliterated and the sphenoid sinuses entirely gone.

skin and scanty distribution of hair over the body. There was a primary optic atrophy on both sides, more advanced on the left than on the right side. The neurologic examination revealed no abnormalities. The Wassermann reaction of the blood was negative. Roentgenograms of the skull showed complete destruction of the sella turcica, with erosion of the floor. The posterior clinoid processes were practically gone. Apparently the growth had gone through the floor of the sella turcica into the sphenoid sinuses (fig. 5).

He was given a course of high voltage roentgen therapy consisting of doses of 150 or 200 r four times a week for three weeks during October and November 1929, and in January 1930 a shorter similar course for two weeks. He showed considerable improvement in the visual fields (fig. 5). This improvement, however, soon began to fail, and he went to the Mayo Clinic on April 24, 1930, where he was operated on by Dr. Learmonth on May 2. An adenocarcinoma of the pituitary gland was found. A decompression area was provided. Following operation the patient was given three courses of high voltage treatment, the first from May 16 to May 20, the second from July 8 to July 11 and the third from September 8 to September 11. He was also treated by radium between October 7 and October 21. He returned to the Mayo Clinic in December 1930, at which time his vision was continuing to fail (fig. 5).<sup>19</sup>

*CASE 6.—Pituitary tumor; probable chromophobe adenoma (unverified) in an adolescent boy. Bitemporal hemianopia; headaches; hypopituitarism. Definite improvement in fields and headache following high voltage therapy.*

J. O. Jr., a boy, aged 16, a student, was referred by Dr. George W. McCoy, Los Angeles, on Nov. 1, 1929. For a year previously his vision had not been good. A bitemporal hemianopia was found on the first examination (fig. 6). Two months prior to examination he had troublesome headaches, which kept him from school. The headache was principally occipital.

Examination revealed a boy, 4 feet, 11 inches (149.8 cm.) tall, weighing 95 pounds (43 Kg.). He was undersized and distinctly of the feminine type. Secondary sexual characteristics had not developed. There was no evidence of hair on the body, and a beard had not started to grow. His voice was high-pitched. The skin was smooth, soft and dry. The eyegrounds showed a double primary optic atrophy with sharply outlined disks and marked pallor. The blood vessels were in good condition. The Wassermann reaction of the blood was negative. Roentgenograms of the skull showed marked enlargement of the sella turcica, with thinning of the posterior clinoid processes (fig. 6).

He was given two courses of high voltage therapy, following which there was marked improvement in the visual fields. The fields recorded on Aug. 28, 1931, showed approximately the maximum amount of improvement (fig. 6). The headaches disappeared. He returned to school, and the improvement of vision was still maintained after three years. In October, 1931, he was 5 feet, 5 inches (165.1 cm.) tall, weighed 111 pounds (50.3 Kg.) and was beginning to show signs of secondary sexual development.

Doses of 150 r four times a week were given continuously over a period of seven weeks in the first course, without any serious reaction or occasion to reduce the treatments. The second course, four months later, was short, and unfinished, and probably had little influence on the result.

*CASE 7.—Pituitary tumor; probable chromophobe adenoma (unverified). Bitemporal hemianopia; amenorrhea. Improvement of visual fields and acuity following irradiation. Amenorrhea uninfluenced.*

M. J., a woman, aged 32, unmarried, a stenographer, was referred by Dr. E. Richmond Ware, Los Angeles, on March 13, 1930. She first noticed failing

19. Dr. A. W. Adson of the Mayo Clinic provided the details regarding this patient's course while under observation at the clinic.

vision in the left eye in July 1929. This took the form of a temporal hemianopia. She did not recall when visual difficulties began in the right eye, but early in 1930 she became conscious of the fact that she could not see normally on that side. The visual fields taken at first examination showed a temporal hemianopia on the right and loss of vision, save for the upper nasal quadrant, on the left (fig. 7).

Examination revealed a woman about 5 feet, 7 inches tall, weighing 150 pounds. The neurologic examination revealed nothing important. The eyegrounds showed a primary optic atrophy on each side, but with fairly large arteries and veins persisting. Amenorrhea started at the age of 30. The Wassermann reaction of the

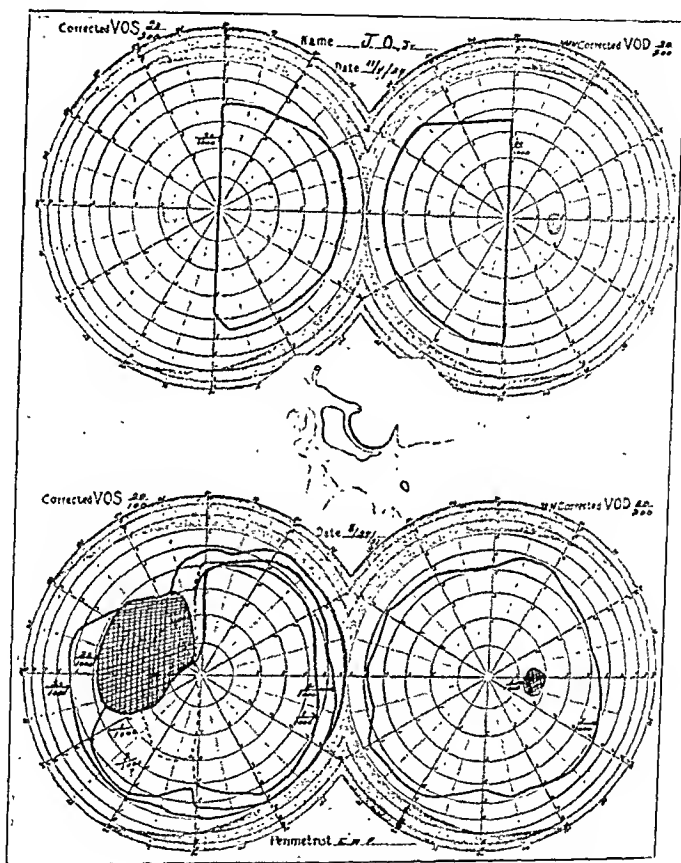


Fig. 6 (case 6).—Chromophobe adenoma (unverified). Above are the visual fields showing typical bitemporal hemianopia before irradiation, and below, the marked improvement following two courses of high voltage therapy. The insert shows moderate enlargement of the sella turcica with thinning of the posterior clinoid processes and beginning invasion of the sphenoid sinuses.

blood was negative. Roentgenograms of the skull showed moderate enlargement of the sella turcica and attenuation of the posterior clinoid processes (fig. 7).

A course of high voltage therapy was started on March 18. Within a few days the patient had headaches and showed marked contraction of visual fields, so that by April 3 the right field amounted to a small area of vision on the nasal side, and vision in the left eye was confined to a small area in the upper nasal quadrant. In spite of this, irradiation was continued, and the first course com-

pleted on April 28. Following a similar course of treatment in July and August there was marked improvement in the fields, which remained stationary for more than three years (fig. 7). Visual acuity improved on the right from 20/100 to 20/30.

*Comment.*—Although this patient's visual fields showed contraction during the early course of the high voltage therapy the treatment was continued in 150 r doses three times a week for six weeks. Treatment was then stopped for two months, after which a second, almost identical, course covering another period of six weeks was given. During the

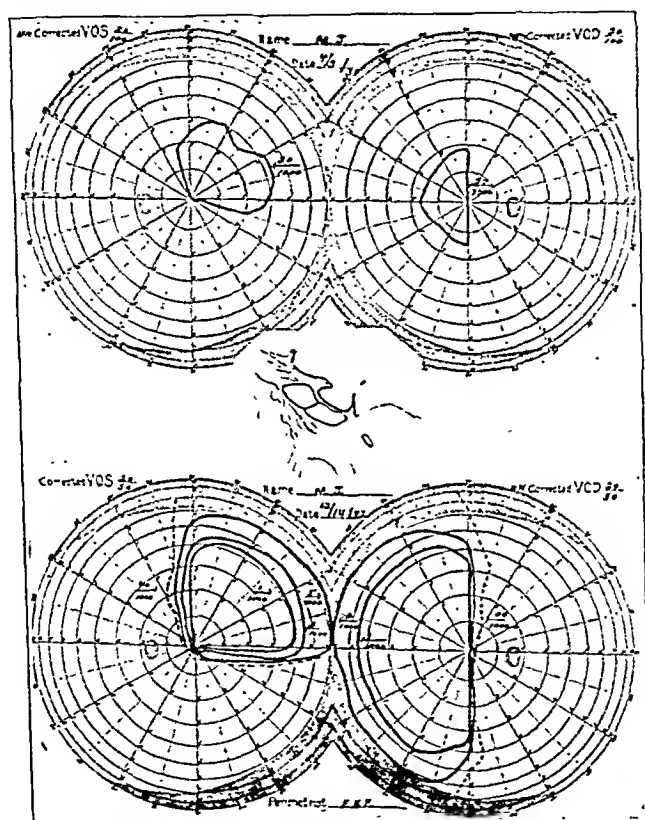


Fig. 7 (case 7).—Chromophobe adenoma (unverified). Above, the fields show the condition two weeks after the first course of irradiation was started. Constriction was temporarily increased as a result of irradiation. Below, the fields show the condition two years later following the second course of irradiation. The gain of vision has been maintained for more than three years. The insert shows the sella turcica moderately enlarged, with beginning erosion of the posterior clinoid processes.

second series of treatments the patient had no untoward reactions. The headaches disappeared. Should diminution of the fields occur again, further irradiation, if necessary followed by partial extirpation of the gland, will be carried out.



disks, but fairly full arteries and veins. The neurologic examination revealed nothing of importance. The Wassermann reaction of the blood was negative. Roentgenograms of the skull showed practical obliteration of the posterior clinoid processes, with depression of the floor of the sella turcica into the sphenoid cavity, so that the latter was almost absent. The sellar cavity was greatly enlarged, about five or six times its normal size (fig. 8).

The fields improved appreciably following a course of high voltage therapy given elsewhere, reaching their maximum about July 6, at which time a bitemporal hemianopia existed. More than this was never attained. Following a further moderate course of high voltage treatment the fields failed to improve, and on November 19, six weeks after the last treatment, an exploratory operation was performed. A chromophobe adenoma was found and partially removed. The wound healed by first intention, but after ten days or two weeks it broke down in places, and subsequent healing was slow.

*Comment.*—This patient had had an indeterminate amount of irradiation elsewhere, prior to coming to us. She had some loss of hair. During August and September 1931, she was given twenty doses of 150 r. The intervals were irregular owing to severe headaches and the patient's inability to come to the laboratory. Following the partial removal of the adenoma her vision again improved (fig. 8), and the improvement, while not as much as could be wished, remained stationary for more than two years. Surgical intervention in this case was more beneficial than high voltage irradiation.

*CASE 9.—Pituitary tumor; probable cystic chromophobe adenoma (unverified). Bitemporal hemianopia. Continued loss of vision in spite of irradiation. Surgical intervention refused.*

R. C. H., a man, aged 39, married, a bookkeeper, was referred by Dr. Carl Fisher, Los Angeles, on Sept. 13, 1930. Two years previously he began to have failing vision in the right eye. This increased. He did not know that there was failure of vision of the left eye until a bitemporal hemianopia was found by Dr. Fisher on September 1. The patient had never been subject to headaches. Visual fields taken on September 15 showed a bitemporal hemianopia with low acuity in the left eye (fig. 9).

Examination revealed a man 6 feet (182.8 cm.) tall, weighing 190 pounds. He showed practically no signs of pituitary disorders. There was a primary optic atrophy on each side, more marked on the right than on the left. The arteries were smaller on the right than on the left. The deep reflexes on the left were a little quicker than on the right, but otherwise neurologic examination revealed nothing relevant. The Wassermann reaction of the blood was negative. Roentgenograms of the skull showed an enlarged sella turcica, with the enlargement chiefly forward and downward. There was some thinning of the posterior clinoid processes. The sphenoid sinuses were clear, but narrower than normal (fig. 9).

The patient was given a course of high voltage therapy from September 18 to November 6, with slight temporary improvement, but by December 31 vision had again failed, so that one was unable to chart the left side accurately, and what vision remained on the right side appeared to be in the upper nasal quadrant (fig. 9). Exploration of the pituitary region was strongly urged, but was refused. The patient has not been seen since.

*Comment.*—The patient was treated with doses of 150 r three times a week for seven weeks, except for the third, when he did not receive a treatment. As no benefit was derived, it was felt that the tumor was cystic. An exploratory operation should, of course, be performed.

**CASE 10.**—*Pituitary tumor; probable cystic chromophobe adenoma (unverified). Hypopituitarism; atypical bitemporal hemianopia. Temporary improvement following high voltage therapy.*

O. J. O., a man, aged 40, married, a plumber, was admitted to the Los Angeles County General Hospital on Oct. 13, 1930. There was an indefinite history of

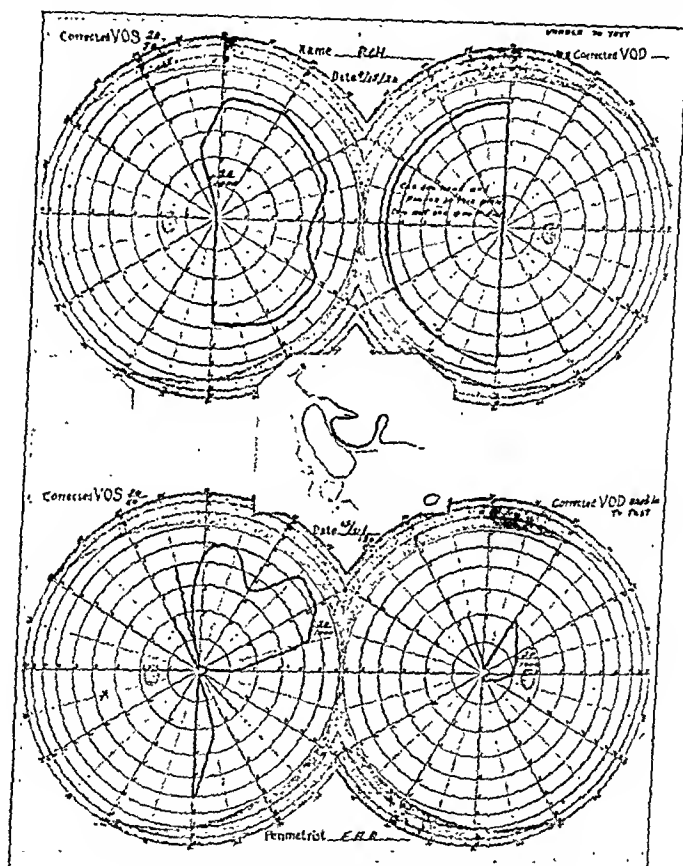


Fig. 9 (case 4).—Cystic chromophobe adenoma (unverified). Above are the perimetric fields when first seen, and below, the fields showing further loss of vision three months later following high voltage therapy. Surgical intervention was refused. The insert is a tracing of the sella turcica showing moderate enlargement of the structure with some clubbing of the posterior clinoid processes and no invasion of the sphenoid sinuses.

polyuria and polydipsia for many years. He drank about twelve glasses of water a day. Four years previously he began to have failing vision, more marked in the left eye. The visual fields, taken on December 16, show atypical bitemporal hemianopia (fig. 10). The patient had been having dull bitemporal and frontal headaches for several weeks previous to the examination.

Examination revealed a man with characteristics of abnormal function of the pituitary gland, about 5 feet, 10 inches (177 cm.) tall, weighing 164 pounds

(74.4 Kg.). The neurologic examination revealed no abnormalities. The eye-grounds showed sharply outlined, pale disks, with prominent optic cupping. The Wassermann reaction of the blood was negative. Roentgenograms of the skull showed the sella turcica to be about four times as large as normal. There was thinning of the floor, which dipped into the sphenoid sinuses. The posterior clinoid processes were thin, and the anterior clinoid processes were distinct (fig. 10)).

He was given high voltage irradiation elsewhere, consisting of insufficient weekly doses from December 1930 to June 1931, and again in November 1931 and in January 1932. The visual fields showed temporary improvement following the treatments and in April 1933 he was given a third course by Dr. Seeley Mudd at

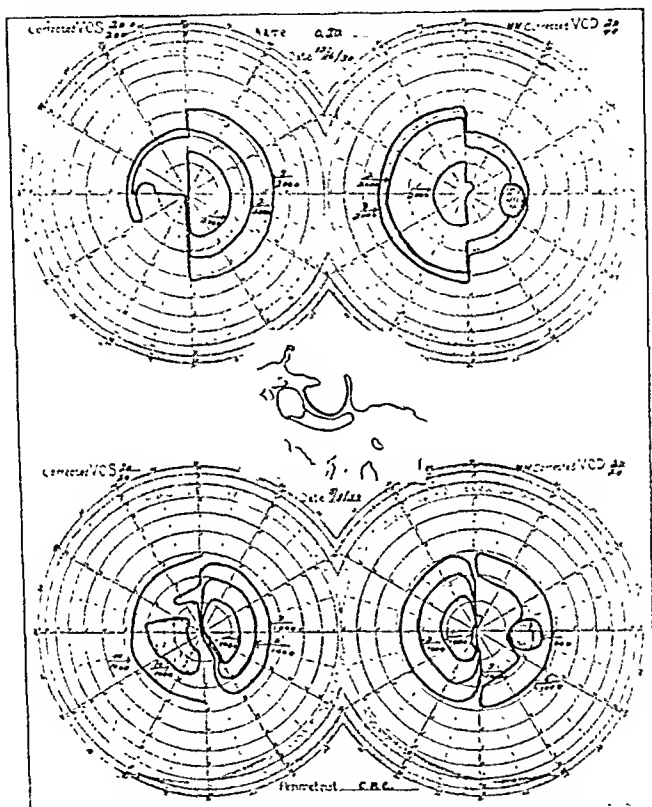


Fig. 10 (case 10).—Chromophobe adenoma (unverified). Above, the fields show the marked defect in the upper and lower temporal quadrants of each, and below is seen the condition of the fields three years later, following three courses of irradiation. The fields have fluctuated back and forth for three years, at times being considerably better than the fields shown below. Operation was refused. The insert shows the sella turcica with considerable thinning of the posterior clinoid processes and deepening of the floor of the sella turcica. The sphenoid sinuses are encroached on posteriorly.

the California Institute of Technology, at which time 600 kilovolts was used. Following this, there has been a little improvement in the fields (fig. 10). He has also had several mild petit mal attacks.

*Comment.*—This man should have an exploratory operation. Irradiation improved his vision only temporarily. The tumor may be a



cystic chromophobe adenoma. In spite of the fact that his vision has not materially improved in the past three years, during which time three courses of high voltage irradiation have been given, he has not lost ground. It is possible that irradiation retarded the growth of the tumor.

CASE 11.—*Pituitary tumor; probable chromophobe adenoma (unverified). Vision in right eye practically gone; temporal hemianopia in left eye. Slight improvement following high voltage therapy.*

M. E. F., a woman, aged 41, married, a housewife, was admitted to the Los Angeles County General Hospital on Aug. 24, 1929. There was a history of failing

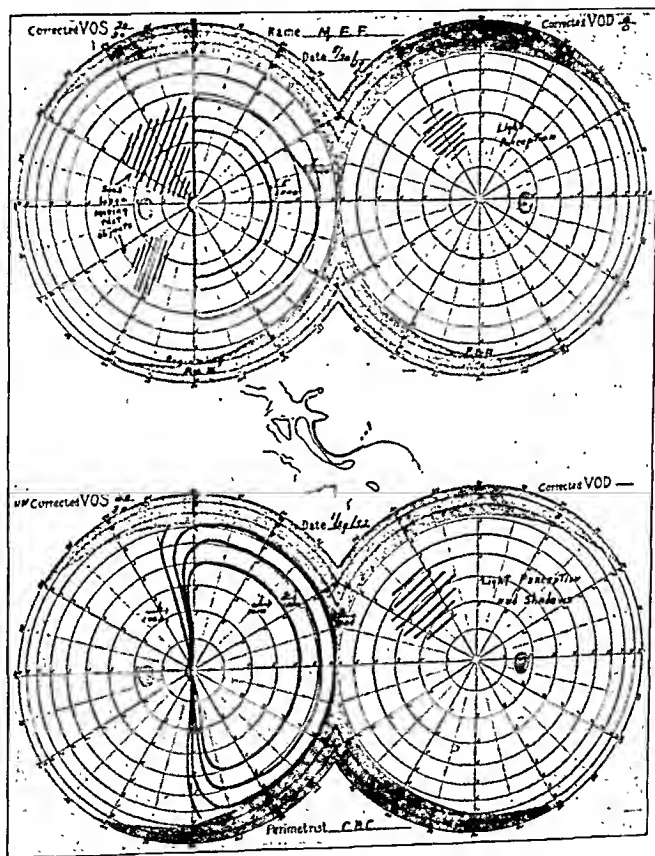


Fig. 11 (case 9).—Chromophobe adenoma (unverified). Above is shown the slight perception of light in the right upper nasal field and the fairly characteristic temporal hemianopia on the left; below the fields show practically the same condition on the right, with moderate improvement on the left three years later. Two courses of high voltage therapy were given, operation having been refused. The insert shows a tracing of an enlarged sella turcica, with almost total destruction of the posterior clinoid processes and marked invasion of the floor in the region of the sphenoid sinuses.

vision for three and a half years previously. Vision in the right eye was practically gone, and vision in the left was so poor that she could not read without using a reading-glass. The visual fields, taken on August 30, showed bare perception of light in the upper nasal quadrant of the right field and a temporal hemianopia of the left (fig. 11). She had never been subject to headaches.

Examination revealed a woman 5 feet, 5 inches tall, weighing 142 pounds (64.4 Kg.), showing no general evidence of disturbance of pituitary function. The eyegrounds showed a double primary optic atrophy and sharply outlined, pale disks. The disk on the right was considerably paler than that on the left. A general neurologic examination revealed no abnormalities. The Wassermann reaction of the blood was negative. Roentgenograms of the skull showed marked enlargement of the sella turcica, with erosion of the dorsum sellae. The posterior clinoid processes had practically disappeared, and the floor of the sella turcica was pushed down well into the sphenoid region (fig. 11).

She was given high voltage treatments elsewhere on October 5, 7 and 16. We are inclined to believe that they consisted of rather massive doses. We were unable to obtain reliable information regarding the exact amount of radiation or subsequent reaction. Following irradiation there have been fluctuations in the visual fields. A field taken on Jan. 29, 1932, showed moderate improvement (fig. 11).

*Comment.*—This patient has been advised repeatedly to have an exploratory operation, but has refused. It is possible that the adenoma has become cystic, as she had little benefit from intensive doses of irradiation.

*CASE 12.*—*Pituitary tumor; cystic chromophobe adenoma (verified). Bitemporal hemianopia; headaches. Temporary improvement following high voltage therapy. Later, partial removal of a cystic chromophobe adenoma.*

G. A. E. R., a woman, aged 44, married, a housewife, was admitted to the Los Angeles County General Hospital on April 30, 1931. She had been having severe frontal and occipital headaches for the previous two years, the principal pain being behind the eyes. Her weight had increased from 160 to 190 pounds (72.6 to 86.2 Kg.). The menopause had occurred eighteen months previously. There had been failing vision for seven months prior to examination, first noticed as a blurring of letters while reading. The left eye was affected more than the right. The failure of vision took the form of a bitemporal hemianopia, as shown by visual fields taken on May 1, 1931 (fig. 12).

Examination revealed a woman 5 feet, 6 inches (167.6 cm.) tall, weighing 190 pounds. There was tapering of the fingers and some coarsening of the skin, and hairy distribution over the body was becoming sparse. She showed typical primary optic atrophy of each eye, more marked on the right than on the left. The right pupil was larger than the left, but otherwise the neurologic examination gave negative results. The Wassermann reaction of the blood was negative. Roentgenograms of the skull showed a marked irregular enlargement of the sella turcica; the anterior clinoid processes were shortened; the posterior clinoid processes were almost completely eroded, and the floor of the sella turcica was irregular and flattened (fig. 12).

She was given a course of high voltage therapy elsewhere, consisting of four small weekly doses in June and July 1931 and a single dose in January 1932. Following this there was considerable improvement in the fields. The last record, taken on December 14, showed greater improvement in the left field than in the right; however, there was still a fairly atypical bitemporal hemianopia (fig. 12). Subsequently the fields became more contracted, and on May 13, 1932, a cystic chromophobe adenoma was partially removed at operation. The fields became normal, but after a year began to contract in the form of a bitemporal hemianopia.

The patient had also gained 35 pounds (15.9 Kg.), weighing, in June 1933, 225 pounds (102 Kg.).

*Comment.*—The recent gain of weight probably indicates an increase of the symptoms of hypopituitary disturbance caused by removal of tissue of the anterior lobe a year previously. Reexploration is being considered because of the return of (her) visual deterioration. Whether further removal of the adenoma will again increase the symptoms of glandular deficiency, already so marked, is an open question.

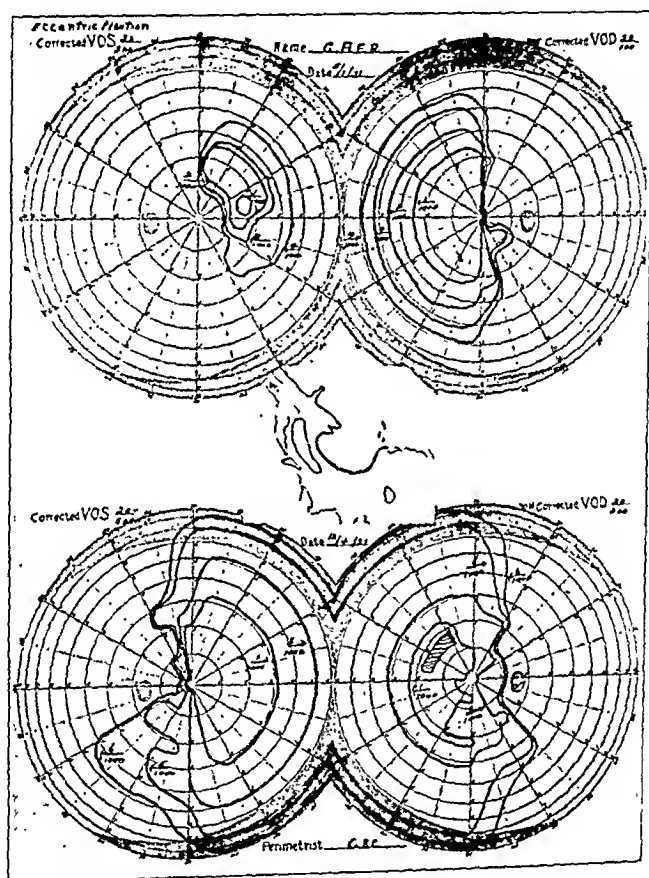


Fig. 12 (case 12).—Cystic chromophobe adenoma (verified). Above, the fields show the condition before high voltage therapy, and below, the improvement following two courses of high voltage therapy seven months later. Full restoration of the fields followed partial removal of the tumor, but a year later contraction again occurred. The insert shows the sella turcica greatly enlarged, with almost total destruction of the posterior clinoid processes and invasion and partial obliteration of the sphenoid sinuses.

CASE 13.—Pituitary tumor; probable chromophil adenoma (unverified). Acromegaly; beginning constriction of visual fields. Improvement of fields following high voltage therapy. Subsequent decompression because of headache.

A. B., a woman, aged 36, unmarried, a school-teacher, was referred by Dr. Philip M. Savage, San Bernardino, Calif., on Sept. 16, 1930. Her principal com-

plaint was pain in the back of the head, neck and shoulders, which had been present for the past five or six years. She had not noticed difficulty in vision, but the fields, taken on September 16, showed general contraction on both sides, the contraction being relatively greater in the temporal field than in the nasal (fig. 13).

Examination revealed a woman 5 feet 2 inches (157.4 cm.) tall, weighing 147 pounds (66.7 Kg.), who showed typical acromegalic changes in her features and extremities. Her hair was very heavy, dry and coarse. The amount of hairy distribution over the body was increased and was of the masculine type. Her hands and feet were large; the size of shoes had increased from 6¼ to 7¼ in the past few years. The eyegrounds showed nothing remarkable. The margins

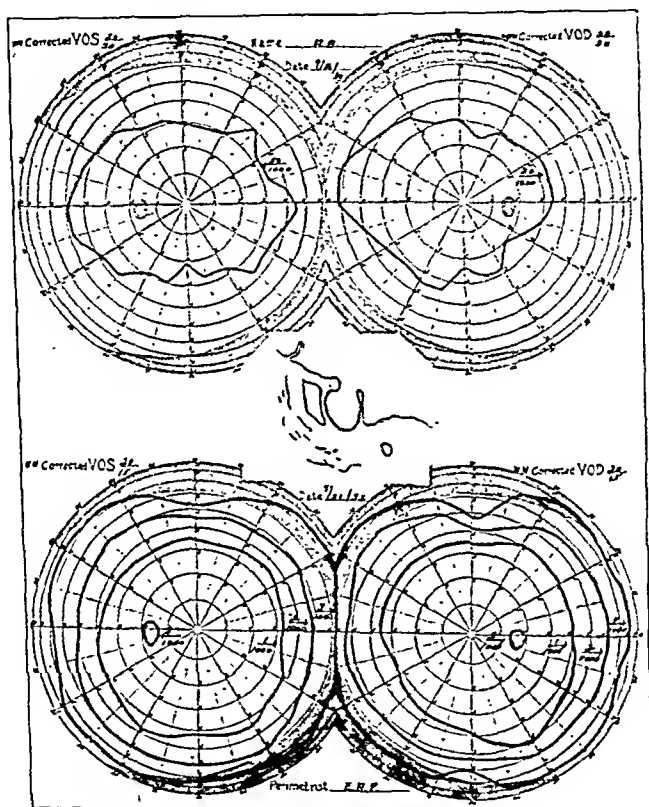


Fig. 13 (case 13).—Chromophil adenoma (unverified). Above are the fields before irradiation, and below, following two courses of high voltage therapy and subsequent subtemporal decompression. The insert shows the sella turcica moderately enlarged, deep and narrow, with thinning of the posterior clinoid processes and clubbing of the anterior clinoid processes. The sphenoid sinuses are definitely encroached on.

of the temporal disk were clear. The nasal margins were somewhat indistinct, and there was some overfilling of the veins. There was no pallor of the disks. Otherwise, the neurologic examination revealed no abnormalities. The Wassermann reaction of the blood was negative. Roentgenograms of the skull showed typical changes of acromegaly, with an unusually thick, dense calvarium. The mandible was heavy. There were enostoses of the frontal bone. The sella turcica

was very large, the major enlargement being downward toward the sphenoid sinuses. The posterior clinoid processes were very thin, but not displaced. The floor of the sella turcica appeared to be intact (fig. 13). Roentgenograms of both hands failed to show tufting of the terminal phalanges.

She was given a course of high voltage therapy consisting of doses of 150 r five times a week during September 1930, with marked improvement in the visual fields. Following this, there was an increase of her headaches. This continued during the following year. From July 2 to July 20, 1932, she was given a similar course of 150 r daily for eighteen days, not because of constriction of the visual fields, but because of headache. Fields taken after this (fig. 13) remained essentially normal. The headaches continued, and on August 22, a simple right subtemporal decompression was carried out. The tissues were unusually vascular, although the intracranial pressure was not increased. It was felt that the vascularity of the tissues might be secondary to the last course of irradiation, which was completed less than five weeks before the operation. The sellar region was not examined, as there were no neighborhood signs of pressure. She returned to her teaching duties, and reported that the headaches were in no way improved. Although she presented no neighborhood symptoms, the continuance of headache may in the future lead us to explore the chiasm. Should a distended diaphragma sellae be found, relief from distention might be followed by an improvement in the headaches. On the other hand, many patients with acromegaly have been reported who have gone through life with continued headache, although they did not otherwise show signs of generally increased intracranial tension or undue pressure on the chiasm.

*Comment.*—This patient underwent both courses of treatment exceedingly well; the doses, though small, were given more rapidly and more steadily than in most cases of the series. The acromegalic features of the case have not increased during the past two years.

*CASE 14.—Pituitary tumor; chromophobe adenoma (verified). Bitemporal hemianopia, with improvement following high voltage therapy. Death due to cerebral hemorrhage.*

P. E. E., a man, aged 68, married, an agricultural inspector, was referred by Dr. C. B. Walker, Los Angeles, on Sept. 27, 1930. His only complaint was failing vision, which had first been observed eighteen months previously. This was called to his attention while doing fine printing. By July 1930 he was unable to pass an examination for his automobile license owing to difficulty in reading. Visual fields taken on September 27 by Dr. C. B. Walker (fig. 14) showed a fairly typical bitemporal hemianopia, more advanced on the right than on the left. He did not complain of headache at any time.

Examination revealed an elderly man 5 feet, 7 inches tall, weighing 144 pounds (65.3 Kg.). He showed slight evidence of hypopituitary disturbance. His beard was very light, and the hairy distribution over the body was scant. There were no lunulae of the fingernails. The eyegrounds showed both disks to be sharply outlined and a little paler than normal. The lamina cribrosa was distinct. The right disk was paler than the left. The neurologic examination gave negative results. The Wassermann reaction of the blood was negative. Roentgenograms of the skull showed enlargement of the sella turcica, with almost complete absorption of the clinoid processes. Several shadows were seen which were suggestive of a cyst wall (fig. 14).

The patient was given a course of high voltage therapy consisting of doses of 150 r three times a week for six weeks, ending November 14, with marked improvement in his visual fields, as shown by Dr. Walker's chart taken on Feb. 17, 1931 (fig. 14). He returned to work, and apparently was in good health, until one year later, when he died of a cerebral hemorrhage on Dec. 24, 1931.

A report of the autopsy, performed by Dr. G. D. Maner, contained the following: On reflecting back the cerebrum after incising the dura, there was found an irregular lobulated mass located beneath the dura and occupying the sella turcica. The optic chiasm lay just anterior to it, and was greatly elongated and distorted, especially the left fork; the posterior portion lying over the tumor was

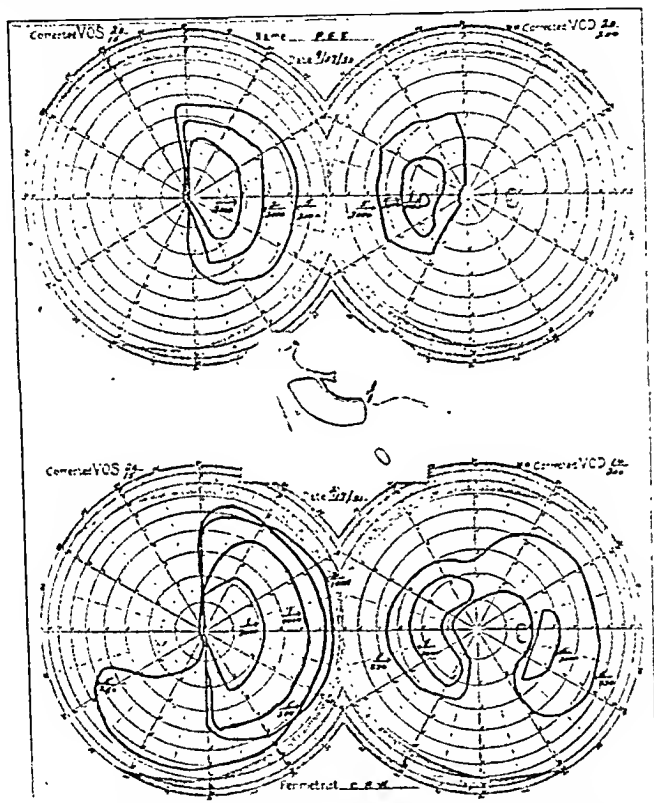


Fig. 14 (case 14).—Chromophobe adenoma (verified). Above, the fields show marked constriction in the form of a bitemporal hemianopia before irradiation, and below, definite improvement six months later. The insert of the sella turcica shows almost complete destruction of the posterior clinoid processes and marked blunting of the anterior clinoid processes. The shallow type of sella turcica shows little, if any, invasion of the sphenoid region.

greatly widened. There was a concavity on the inferior surface of the cerebrum, between the peduncles and the chiasm, which conformed to the shape of the tumor. Both ophthalmic arteries, as well as the third, fourth and sixth cranial nerves on both sides were elongated, widened, distorted and displaced laterally.

The tumor involved the whole of the hypophysis and weighed 18.5 Gm. Its measurements were: width, 5 cm.; anterior posterior diameter, 4 cm., and greatest thickness, 3 cm. It was roughly bilobed, with the right lobe approximately twice

the size of the other. The overlying dura was intact. The surface was smooth, but the greater part of the anterosuperior aspect was blood stained. The consistency was liver-like, but the hemorrhagic portions were softer. The sectioned surface was smooth; the greater part was a dull, gray-pink, but along the anterior portion and on the whole length of the right lobe was an area of diffuse hemorrhagic extravasation.

The sella turcica was greatly widened in all dimensions; the normal contour was missing, the outline being perfectly flat. The dimensions were: length, 4 cm.; width, 3.75 cm. The floor was intact and the sphenoid cells were of normal outline. The posterior and anterior clinoid processes were absorbed.

On microscopic examination the sections showed an anterior lobe struma. The follicles were greatly increased in number; many were small, but others were of normal size. Practically all were compact and filled with chief, or chromophobe, cells, with only an occasional eosinophil cell. The cells were rounded or short cylindric. The follicles were surrounded by thin septums of connective tissue containing thin-walled capillaries. These appeared to be normal, as compared with a normal gland. No histologic evidences of a malignant process were found.

The diagnosis was: chromophobe adenoma of the pituitary gland; cerebral arteriosclerosis, and recent hemorrhage in the left temporal lobe of the brain.

"No changes in the histologic picture were seen to suggest that irradiation had any effect on the tumor in the way of interstitial or cellular changes."

*Comment.*—In this instance improvement to serviceable vision was obtained in a chromophobe adenoma. The accidental death from apoplexy more than a year later gave an excellent opportunity to study the pituitary gland. No histologic changes were found at this late date which could be ascribed to irradiation.

*CASE 15.—Pituitary tumor; probable chromophobe adenoma (unverified). Bitemporal hemianopia. Improvement in fields following high voltage therapy.*

J. F. K., a man, aged 47, married, a barber, was referred by Dr. J. Ross Reed, Pasadena, Calif., on Dec. 26, 1930, with a diagnosis of tumor of the pituitary gland. For ten years previously there had been some difficulty in seeing with the left eye, and about five months previously he noticed failing vision in the right eye. He now had difficulty in seeing well enough to cut hair or shave patrons. A visual field taken on December 26 (fig. 15) showed a typical bitemporal hemianopia, with marked constriction of the nasal fields and lowered visual acuity. He had not complained of headache at any time.

Examination revealed a man 6 feet tall, weighing 200 pounds (90.7 Kg.). He showed definite characteristics of hypopituitary disturbance, such as dryness of the skin and scantiness of hair over the face and body. Although a large man, he did not appear to be acromegalic. The eyegrounds showed the margins of the disks to be indistinct, with overfilling of the veins, but no measurable elevation. The disks seemed somewhat paler than normal. It was not a clearcut picture of primary optic atrophy. The right pupil was larger than the left, but the neurologic examination was otherwise irrelevant. The Wassermann reaction of the blood was negative. Roentgenograms of the skull, taken on December 26, revealed a definite enlargement of the sella turcica, with practically a loss of the posterior clinoid processes. The floor of the sella turcica was depressed toward the sphenoid bone. It was difficult to get a clear view of the pituitary gland, because of massive mastoid cells (fig. 15).

The patient was given a course of high voltage therapy consisting of doses of 150 r three times a week for two and a half weeks, ending Jan. 14, 1931, and a similar course from March 20 to April 7, with considerable improvement in the fields. The man had a head of a large diameter, and the amount of dosage delivered at the tumor was smaller than the average. The last field, taken on Oct. 25, 1932, approximately two years later, still showed a hemianopia on the right, but enlargement of the fields in both the upper and the lower temporal quadrants on the left. The visual acuity was unchanged.

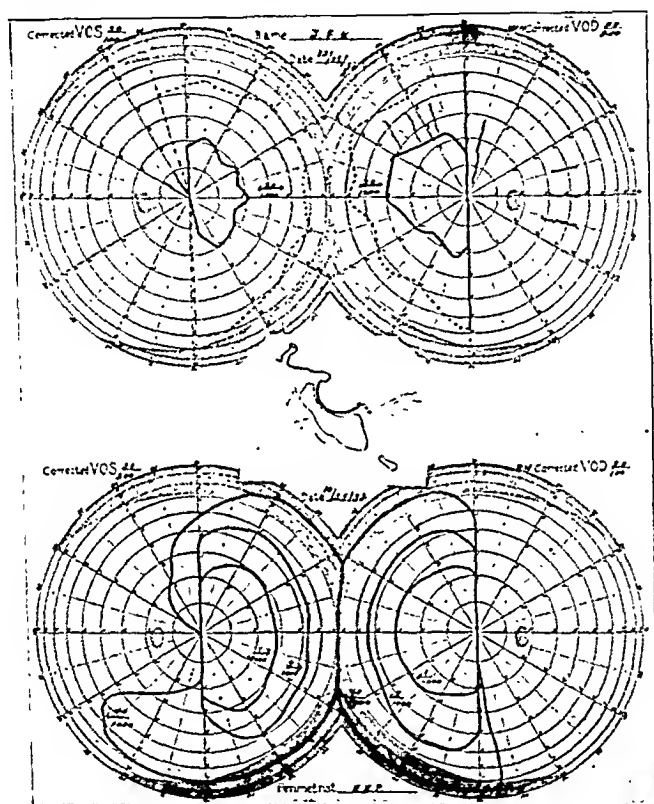


Fig. 15 (case 15).—Chromophobe adenoma (unverified). Above is seen the marked contraction of both fields in the form of a bitemporal hemianopia before irradiation, and below, the improvement two years later, following two courses of high voltage therapy. The insert shows the sella turcica which was moderately enlarged, with almost complete destruction of the posterior clinoid processes and moderate invasion of the sphenoid sinuses.

*Comment.*—This patient later moved to Oakland, Calif., and is under the care of Dr. Howard C. Naffziger, San Francisco, who reported on May 22, 1932, that "his fields are purely those of a bitemporal hemianopia at present." Dr. Naffziger determined to keep the patient under monthly observation, and if his acuity or field decreased to advise an operation. The patient undoubtedly had an insufficient amount



of irradiation while under our observation; if the dosage had been more intensive and additional courses given, further improvement might have been obtained.

CASE 16.—*Pituitary tumor; probable chromophobe adenoma (unverified). Marked headaches and bitemporal hemianopia; improvement of both following high voltage irradiation.*

E. H. G., a man, aged 42, married, an automobile mechanic, was referred by Dr. H. L. Hatfield, Pasadena, Calif., on May 20, 1931. He had been complaining of failing vision for four or five years previously, and a bitemporal hemianopia

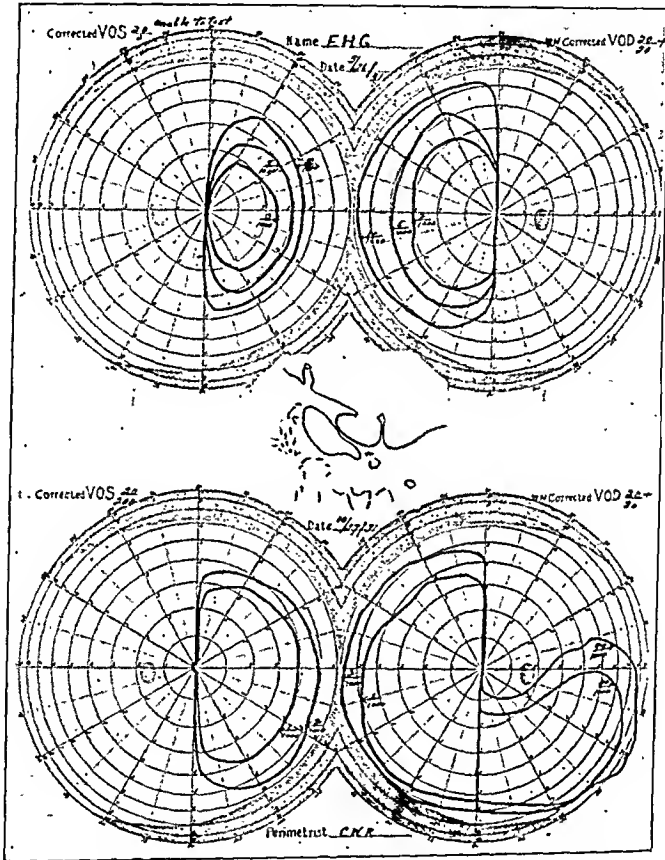


Fig. 16 (case 16).—Chromophobe adenoma (unverified). Above is seen a bitemporal hemianopia with marked contraction of the temporal fields on the left prior to irradiation, and below, the improvement six months later, especially on the right, following two courses of high voltage therapy. The insert is a tracing of the sella turcica showing moderate enlargement, with thinning of the anterior and posterior clinoid processes. The sphenoid sinuses are moderately narrowed posteriorly.

had developed two years previously. Vision in the left eye was more impaired than that in the right, as shown by the visual field taken on May 26 (fig. 16).

Examination revealed a medium-sized man. For ten days previous to the examination he had had severe headaches, accompanied by nausea and vomiting.

The headaches were improved and nausea and vomiting ceased following the administration of hypertonic solution of dextrose intravenously. The left disk was sharply outlined and very pale; the right disk was hazy, the veins were congested, a fresh hemorrhage was present in the upper temporal quadrant, and the disk itself was somewhat paler than normal. The right knee jerk was quicker than the left, and there was a positive and well sustained ankle clonus on the right side. Otherwise the neurologic examination gave negative results. The Wassermann reaction of the blood was negative. Roentgenologic examination of the skull showed a much thinned, considerably enlarged sella turcica, about twice the normal size. The posterior clinoid processes were present, but greatly thinned; the floor of the sella turcica encroached on the sphenoid sinuses (fig. 16).

The patient was given two courses of high voltage therapy consisting of average daily doses of 145 r for two weeks, and six weeks later a similar course, by Dr. Carl H. Parker, Pasadena, with marked improvement in the fields, as shown by the record made on October 27 (fig. 16).

*Comment.*—This man was bedridden when first seen, having severe headaches and projectile vomiting. An exploration of the pituitary region was advised, but was refused. Although we feared there would be a serious reaction, he was given high voltage therapy. Previous to irradiation he was dehydrated, and hypertonic solution of dextrose was given intravenously. No reaction followed the irradiation. Whether the dehydration was a factor in this is speculative. Radiation was given more rapidly and intensively than in any other case in the series, with marked improvement of the fields more than five months later (fig. 16). Three years later he was at work, with serviceable vision and complete relief from the headaches.

*CASE 17.—Pituitary tumor; probable chromophobe adenoma (unverified). Marked enlargement of sella turcica; bitemporal hemianopia; hypopituitarism. Considerable improvement in visual fields following two courses of high voltage therapy.*

L. T., a man, aged 39, in the furniture business, was referred by Dr. J. M. Schmoele, Los Angeles, on Oct. 1, 1931. There was a history of failing vision for about a year previously, both eyes being affected, but the left more than the right. The visual fields, on first examination, showed a typical bitemporal hemianopia. The left field showed more loss than the right. Visual acuity was: left, 20/200; right, 20/40 (fig. 17). He also gave a history of previous headaches which at times were severe and accompanied by nausea and vomiting. He had a typical syndrome of hypopituitary disturbance, with loss of libido and a tendency to be drowsy and to tire easily. He also showed fairly characteristic changes in the skin.

Examination revealed a man with typical signs of hypopituitary disturbance; he was of medium size and build, with a soft, dry skin and a scarcity of hair as regards the beard and other parts of the body. There was bilateral primary optic atrophy with sharp-cut disks, which were only moderately pale. The retinal arteries and veins were of good caliber. The general neurologic examination revealed no abnormalities. The Wassermann reaction was negative. Roentgeno-

grams of the skull showed a somewhat enlarged sella turcica with fairly normal anterior clinoid processes; the posterior clinoid processes were practically destroyed, the shadow of only one being definitely made out. The floor of the sella turcica was not particularly depressed (fig. 17).

*Comment.*—The patient was given two courses of high voltage therapy, the first of 150 r every second day covering two weeks, ending Oct. 23, 1931, and the second a similar course ending March 20, 1932. The doses were small, the courses short and the total amount

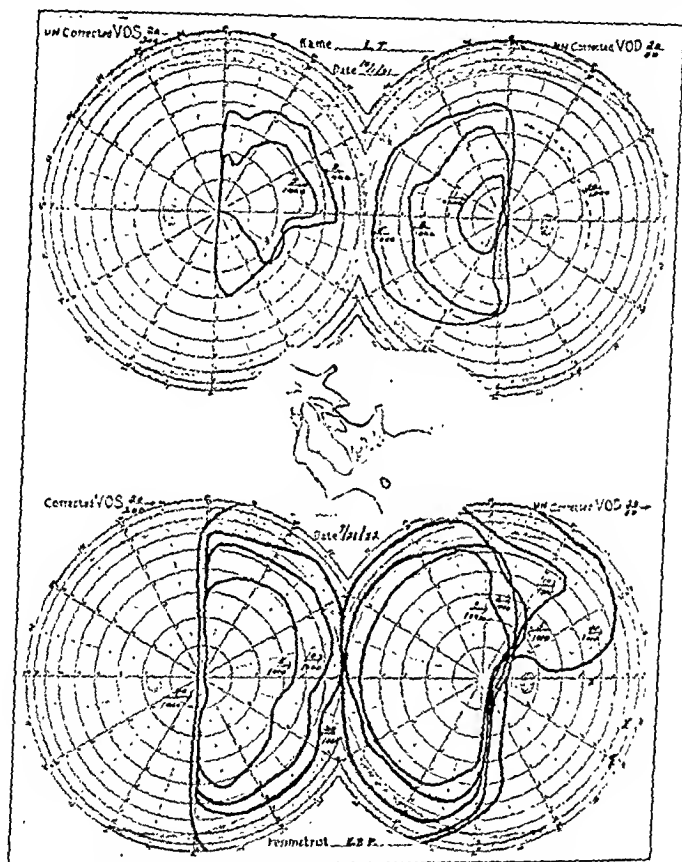


Fig. 17 (case 17).—Chromophobe adenoma (unverified). Above, the fields show the typical bitemporal hemianopia before high voltage treatment, and below, improvement in the fields approximately one year later, following two courses of high voltage therapy. The insert shows the sellar region, with the sella turcica but little enlarged and fragmentation of the posterior clinoid processes. The sphenoid sinuses are a peculiar multiloculated type.

unsatisfactory. Following the high voltage therapy he had a fluctuating course. On the whole, there was improvement in the fields (fig. 17). At times, however, they regressed considerably. He adopted Christian science, and did not report after Dec. 12, 1932. An exploratory operation should probably be carried out.

CASE 18.—*Pituitary tumor; probable chromophil adenoma (unverified). Acromegaly. Vision of right eye confined to upper nasal quadrant. Practically blind in left eye. Unsuccessful attempt to remove tumor; decompression. Marked improvement of vision following high voltage therapy.*

E. L. B., a man, aged 44, married, district manager for an electric company, was referred by Dr. F. X. Ammann Jr., Los Angeles, on Oct. 3, 1931. Four years previously he began to have failing vision and violent headaches. A Wassermann reaction of the blood at that time was 4 plus. He improved under antisyphilitic treatment, as to both headaches and vision. One year ago his vision began to fail, and the failure progressed rapidly. On October 6 the visual fields (fig. 18) showed an area of vision in the upper nasal quadrant of the right eye, the left being practically blind. He was having violent headaches at this time.

Examination revealed a man 6 feet tall, weighing 200 pounds, who was definitely acromegalic. The eyegrounds showed both disks to be very pale and sharply outlined. Atrophy on the left side was greater than on the right. The veins were large, but the arteries were exceedingly small. The left pupil did not react to light. The right reacted sluggishly. Otherwise, the neurologic examination revealed no abnormalities. Roentgenograms of the skull showed an enlargement of the sella turcica, with almost complete destruction of the posterior clinoid processes. There was encroachment of the floor of the sella turcica into the sphenoid region (fig. 18).

On October 18, an attempt was made to explore the pituitary gland by a right frontal approach. The brain was under tremendous tension; the right ventricle was apparently collapsed, and it was impossible to secure sufficient room to uncover the chiasm satisfactorily. A decompression of liberal size was performed, and high voltage therapy was instituted two weeks later. The patient has had two courses of irradiation, with marked improvement in the fields and in acuity. This is the only case in which vision returned in a practically blind eye. Fields taken on May 23, 1933 (fig. 18), show that acuity in the left eye is 20/40, and the left field is essentially normal; acuity in the right eye is 20/30 and the field has filled out except for a defect in the lower temporal quadrant.

*Comment.*—The patient had an exploratory operation with decompression before treatment was started, and as a result, a larger dosage, given more rapidly, was possible. He was treated nearly continuously each day for four weeks, with 200 r at each dose. No treatment was given then for five weeks, at which time he was given a second similar course for three weeks. He had no unpleasant reaction.

During October 1933, he began again to show slight constriction of the temporal fields. Consequently, it was considered advisable to give another course of high voltage irradiation. Twelve treatments of 300 r each were given every other day between October 26 and November 20, without disagreeable reaction except for a slight headache following the first two treatments. The decompression area is growing smaller, and apparently new bone proliferation is taking place along the edges of the defect. This may in some way be associated with the acromegaly, and the argument could be used that the acromegaly is advancing.

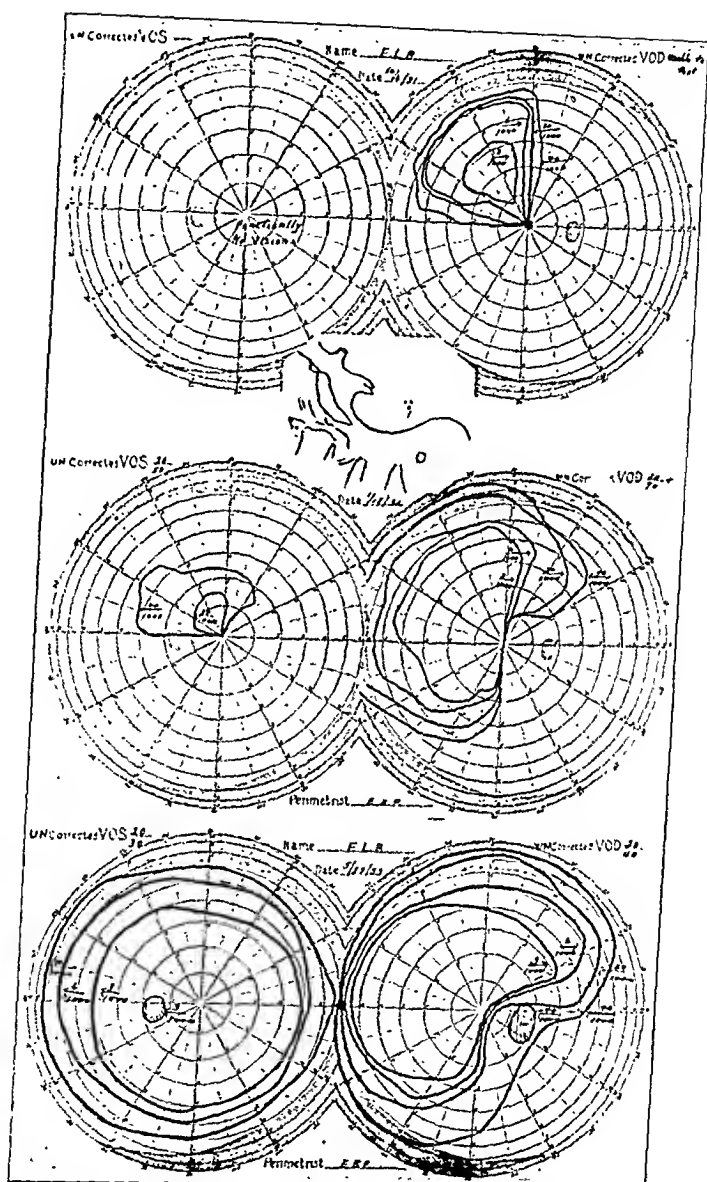


Fig. 18 (case 18).—Chromophil adenoma (unverified). The upper charts show vision remaining in the upper nasal quadrant in the right eye, with practically no vision in the left eye, before decompression followed by high voltage therapy. The middle chart shows improvement three months later in the right field and beginning return of vision in the left upper temporal and nasal quadrants. The lower chart shows further improvement in the fields which still obtained two years later. The insert shows enlargement of the sella turcica, with almost complete destruction of the posterior clinoid processes and invasion of the floor of the sella turcica into the region of the sphenoid sinuses.

CASE 19.—Pituitary tumor; probable chromophobe adenoma (unverified). Atypical hemianopic defect of visual fields. Headaches. Considerable improvement in right eye; continued loss of vision in the left eye following two courses of high voltage therapy.

N. L. A., a man, aged 49, a farmer, was referred by Dr. Charles A. Lindquist, West Los Angeles, on Feb. 3, 1932. His principal complaint was failing vision for the previous five years. This was increasing. Repeated change of glasses had failed to improve his vision. Three years previously he began to have bitemporal headaches, which had continued. At times they were severe, giving him a sense

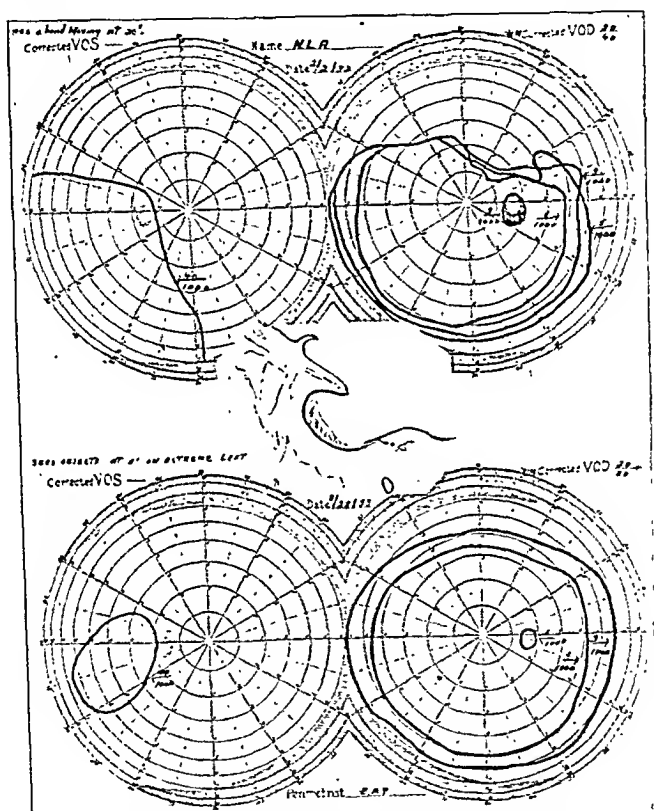


Fig. 19 (case 19).—Chromophobe adenoma (unverified). Above are the visual fields before irradiation; below, the fields one year after irradiation. Vision on the right has definitely improved, and on the left has failed. The insert shows an enormous sella turcica, with complete obliteration of the posterior clinoid processes; the floor of the sella invades the sphenoid sinuses.

as though the left eyeball were being pushed down. During the severe headaches, the vision was much worse.

Examination revealed a man, 6 feet tall, weighing 225 pounds. His father, mother, two brothers and one sister were large. He showed no acromegalic tendency. The eyegrounds showed a double primary optic atrophy, with sharply outlined disks which were definitely pale. The atrophy of the left disk was more marked than that of the right. The veins were of average size, the arteries small.

The visual fields showed an upper nasal and temporal defect of the right eye and a large lower temporal defect of the left eye. The visual acuity on the right was 20/40, and on the left so poor that he could see only movements of the hand at 20 feet (6 meters) and the largest disk, 40 mm., at 1 meter (fig. 19). The Wassermann reaction of the blood was negative. Roentgenograms of the skull showed an enormous enlargement of the sella turcica. It was 3.5 cm. from the anterior clinoid processes to the posterior wall of the cavity. The posterior clinoid processes had disappeared. The floor of the sella turcica was absorbed or pushed down so far that the sphenoid sinus was obliterated (fig. 19).

He was given a course of irradiation consisting of daily doses of 150 r for twenty-five days, with marked improvement in the right eye, but without improvement in the left. In fact, the vision in the left eye gradually failed. The fields (fig. 19) show the changes which occurred over a period of fifteen months.

*Comment.*—This patient should have further irradiation and, if necessary, an exploration of the pituitary gland. It is not impossible that the tumor is becoming cystic.

*CASE 20.—Pituitary tumor; probable chromophobe adenoma (grossly described as "a gliomatous tumor" by the coroner). Enlargement of sella turcica. Temporal hemianopia on left and loss of useful vision on right. No improvement following one course of high voltage therapy. Sudden death.*

O. R., a man, aged 32, a laborer, was referred on March 22, 1932, by Dr. John N. Osburn, Los Angeles. Six years previously he first noticed difficulty in seeing. This began in the right eye. It was called to his attention when sighting his gun while hunting. Gradually the visual difficulties increased. At the time of our first examination, vision in the right eye was reduced almost to shadows. On the left there was a typical temporal hemianopia (fig. 20). There was no history of severe headaches, although at times there had been moderate pain in the back of the head and neck. This was particularly true four years previously.

Examination revealed a man about 5 feet, 7 inches tall, weighing 204 pounds (92.5 Kg.). He showed no general characteristics of pituitary dysfunction. The eyegrounds revealed both disks to be sharply outlined and very pale. In fact, the right disk was chalky white. The veins were of average size, but the retinal arteries were much reduced. The neurologic examination revealed nothing of importance. Roentgenograms of the skull showed no particular enlargement of the sella turcica; the floor, however, was depressed, dipping almost into the sphenoid cavity, and the posterior clinoid processes were practically obliterated (fig. 20).

On March 15, at the California Institute of Technology, he had been given one exposure of 600 kilovolt radiation, of 300 r units, delivered in the right temporal region. He failed to return for further treatment. When first seen by one of us (C. W. R.), he was urged to have an exploration of the pituitary gland because of rapid loss of vision. This he refused to permit. He was then given a course of high voltage irradiation, which consisted of ten 200 r treatments, from April 21 to May 11. There was no appreciable improvement in the fields (fig. 20).

He returned to work as a laborer, most of the work being done in a tunnel where a dam was being constructed. According to his physician, one day he became suddenly ill. This was followed by two or three days of acute headache and vomiting; then he suddenly died, on March 30, 1933. The brain was examined by the coroner who reported: "a gliomatous tumor the size of an egg at the base of the brain, partly occupying the sella turcica." This was beyond question a

large pituitary adenoma, probably of the chromophobe variety. Unfortunately, the tissue was not saved for microscopic examination.

*Comment.*—The single treatment of 300 r probably had no appreciable influence on the pituitary gland. The course of treatments given by us was comparable in dosage with that given in the other cases of the series. Following it there was no improvement in his vision. Only nineteen days elapsed from the time of the last treatment until his death. This was hardly sufficient time to state whether improvement might

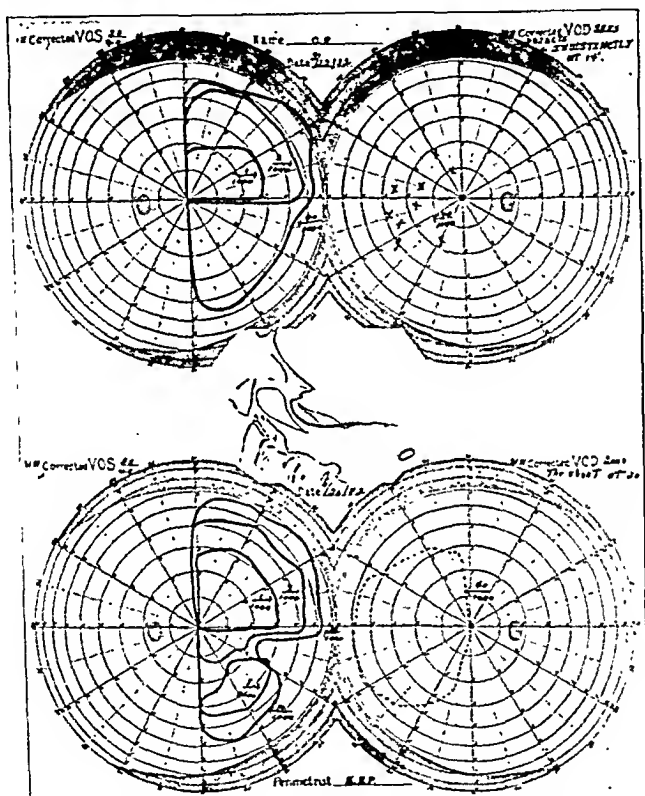


Fig. 20 (case 20).—Chromophobe adenoma (grossly verified). Above are the visual fields before irradiation, showing vision on the right almost gone except for large objects in the nasal field, and below, the absence of improvement of vision two months after one course of irradiation. Operation was refused. The insert shows almost complete destruction of the posterior clinoid processes and invasion of the posterior half of the sphenoid sinuses.

have occurred later. The coroner's report did not tell whether the tumor, as found at autopsy, was cystic or not.

CASE 21.—Pituitary tumor; cystic chromophobe adenoma (verified). Bitemporal hemianopia; headaches; amenorrhea. Continued failure of vision following high voltage therapy. Partial removal of cystic chromophobe adenoma, with return of fields to normal.



A. R., a woman, aged 30, unmarried, a nurse, was referred by Dr. E. C. Jeançon, Los Angeles, on April 19, 1933. Menstruation was established at the age of 13, but amenorrhea developed at the age of 21. About March 1933 she first noticed blurring of the vision, which was soon followed by bitemporal headaches and

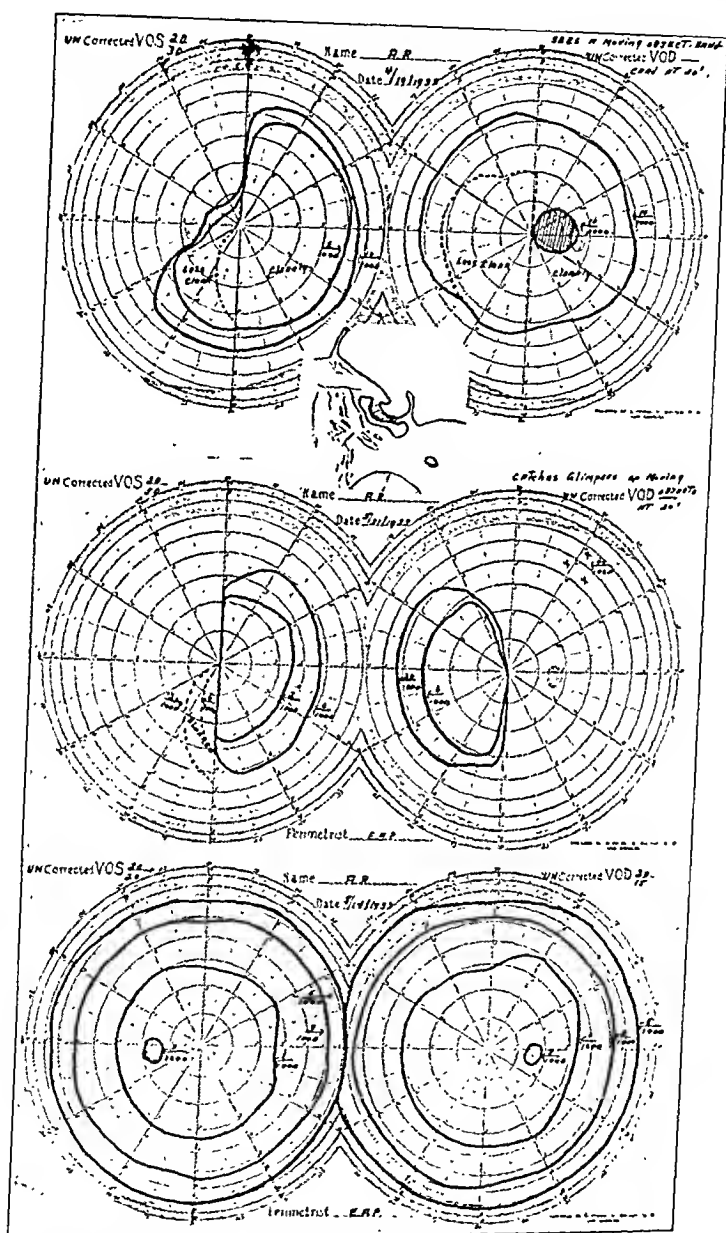


Fig. 21 (case 21).—Cystic chromophobe adenoma (verified). The upper chart shows the condition of the fields when first seen, before high voltage therapy or surgical intervention had been instituted. The center chart shows the advanced constriction following adequate high voltage therapy, and the lower chart reveals the return of the fields and acuity to normal in both eyes following evacuation of a cyst and partial removal of a tumor. The insert shows a moderately enlarged sella turcica, with little, if any, erosion of the anterior or posterior clinoid processes. There is some invasion of the sphenoid sinuses.

occasional dizziness. The visual fields, on April 19, showed considerable contraction on the right, with enlargement of the blind spot and greatly lowered acuity, together with marked temporal constriction on the left, especially in the upper quadrant (fig. 21).

Examination revealed a woman about 5 feet, 8 inches (172.7 cm.) tall, weighing 172 pounds (78 Kg.), who showed rather definite tendencies toward obesity. She had mild symptoms of hypopituitary disturbance. The eyegrounds showed definite pallor of both disks, but the general neurologic examination revealed no abnormality. The Wassermann reaction of the blood was negative. Roentgenograms of the skull showed only moderate enlargement of the sella turcica. The posterior clinoid processes, however, were thinned and eroded, and there was some encroachment of the floor of the sella turcica on the sphenoid sinuses (fig. 21).

She was given 120 r doses through each of three ports, daily for eight days. These were repeated on the third, eighth and twelfth subsequent days, the whole period being about three weeks. Marked erythema developed in one area. Nevertheless, her vision continued to fail rapidly, so that she soon showed a typical bitemporal hemianopia. On the right, the acuity was so low that she could only see moving objects; on the left, 20/50 (fig. 21). An exploratory operation was performed on June 3, at which time a large cystic chromophobe tumor of the pituitary gland was found and emptied. The pathologic diagnosis was cystic chromophobe adenoma. Following partial hypophysectomy the fields began to improve rapidly, and by August 14 had returned to normal.

*Comment.*—This patient was given doses of high voltage irradiation in rapid succession. However, the visual symptoms became more alarming, and an exploratory operation seemed imperative within three weeks of the beginning of treatment. A typical cystic chromophobe adenoma was encountered, following the evacuation of which she made satisfactory progress. She is still amenorrheic. This case bears out the contention that cystic adenomas do not react favorably to high voltage therapy, but respond well surgically. In this case the surgeon feared difficulty from hemorrhage as a result of the recent treatment, but was gratified to find that nothing of the sort occurred.

*CASE 22.—Pituitary tumor; probable chromophil adenoma (unverified). Marked contraction of both fields with bitemporal hemianopic defect predominating. Improvement following high voltage irradiation.*

L. B., a woman, aged 27, married, a housewife, was referred by Dr. Fred S. Modern, Los Angeles, on June 29, 1933. For about a year she had been subject to headaches which were principally bitemporal or frontal. Blurring vision began approximately a year previously, but had increased rapidly during the previous two months. The fields, taken on June 29, showed marked contraction on both sides, with a greater defect in the temporal than in the nasal area (fig. 22). The physical examination revealed nothing suggestive of disease of the pituitary gland except a mild acromegalic look. The nose and lips were full; the general build was rather masculine, and the texture of the skin coarse. The patient had no menstrual disorders. The neurologic examination gave negative results. The eyegrounds showed a well established primary optic atrophy, present on each side. Roentgenograms of the skull showed a definitely enlarged sella turcica, with thinning of the posterior clinoid processes and moderate encroachment of the floor of the sella turcica on the sphenoid sinuses (fig. 22).

A course of high voltage therapy was given which consisted of a series of fifteen doses of 200 r administered almost daily, beginning on June 30 and ending July 16. During the treatment the patient's headaches, if anything, were increased, but not enough to reduce the treatments. She began to notice improvement of her vision within three weeks after high voltage irradiation was started. Figure 22 shows the degree of improvement of the fields on October 30.

*Comment.*—This would appear to be a case of early acromegaly with moderate enlargement of the sella turcica and beginning visual dis-

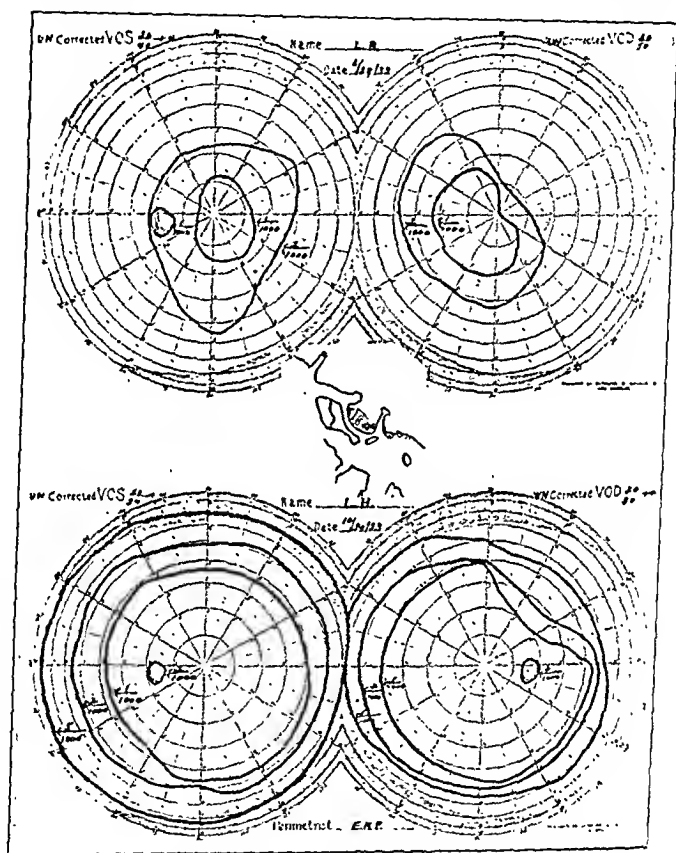


Fig. 22 (case 22).—Chromophil adenoma. Above are the fields taken before irradiation, showing the somewhat bizarre and advanced contraction tending toward a bitemporal hemianopia; below, the fields have returned to normal practically following irradiation. The insert shows a moderate enlargement of the sella turcica, with tufting of the anterior and posterior clinoid processes. There is some invasion on the territory of the sphenoid sinuses posteriorly.

turbances. It is probably a chromophil adenoma, which reacted favorably to high voltage irradiation.

*CASE 23.—Pituitary tumor; probable chromophil adenoma (unverified). Atypical visual fields with nasal hemianopia on the right; marked headaches. Improvement following high voltage therapy.*

B. L., a woman, aged 40, a housewife, was referred by Dr. Leo J. Adelstein, Los Angeles, on Aug. 4, 1933. Approximately three years previously, general

acromegalic changes began to appear. There was enlargement of the hands and feet, together with changes in the features characteristic of the disease. They had continued to develop until examination. Approximately six months previously, it was discovered that she had diabetes mellitus. During the three weeks before examination she had several severe headaches. They were frontal and bitemporal and of short duration. Following her first severe headache she began to see double, and this persisted. She complained of weakness and tired easily. A year before, at the age of 39, amenorrhea occurred. There had been blurring of vision for the entire three weeks.

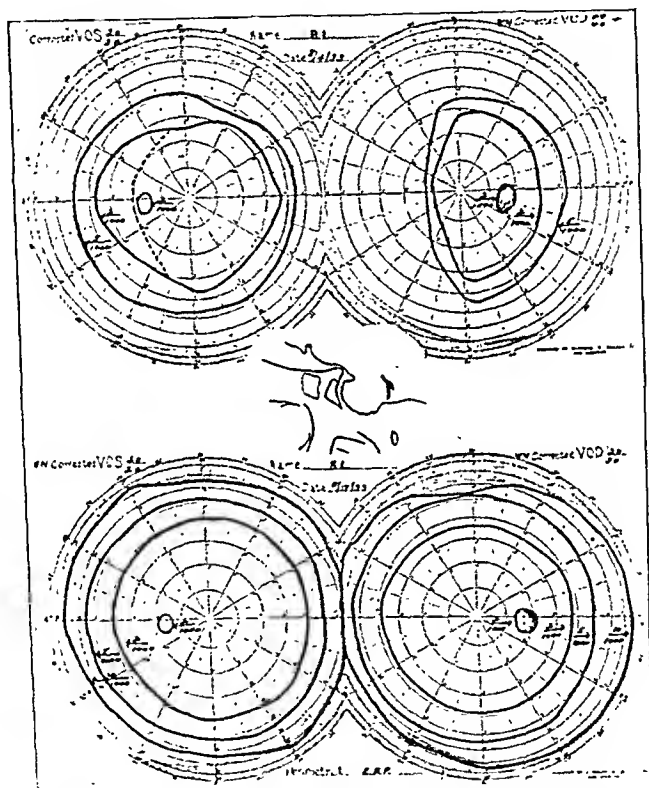


Fig. 23 (case 23).—Chromophil adenoma. Above, the fields show nasal hemianopia on the right and general contraction on the left before irradiation. The dotted line shows temporary constriction of the field occurring during a headache of short duration. Below, the fields show a return to normal following irradiation. The insert reveals the marked enlargement of the sella turcica, with nubbing of the anterior clinoid processes and partial erosion of the posterior clinoid processes. The sellar floor has obliterated the posterior portion of the sphenoid sinuses.

Examination revealed a woman 5 feet, 2 inches tall, weighing 127 pounds. She showed all the characteristics of marked acromegaly, in both her extremities and features. The lower jaw was prognathous, and her build suggested the masculine type. There was a complete palsy of the right abducens muscle. The eyegrounds showed overfilling of the veins, but the disks were not pale. The neurologic examination was unimportant. The Wassermann reaction of the blood was nega-

tive. Roentgenograms of the skull showed enlargement of the sella turcica, with almost complete erosion of the posterior clinoid processes. The floor of the sella turcica was irregular and had broken through into the sphenoid sinuses (fig. 23). The visual fields showed almost complete nasal hemianopia on the right and general contraction on the left. During the charting of the fields a severe headache developed, which lasted about two minutes. During this period a further contraction of the temporal field on the left could be charted, giving a vague left homonymous hemianopic appearance to the picture (fig. 23).

*Comment.*—The patient was given a course of high voltage therapy by Dr. J. Abowitz at the Cedars of Lebanon Hospital. Between August 8 and September 22 she received eleven doses of 300 r through the two temporal areas. The fields, on November 18 had practically returned to normal, the headache had decreased, and the palsy of the right abducens muscle had disappeared.

#### GENERAL COMMENT

Twenty-three cases of tumor of the pituitary gland have been presented, in each of which one or more courses of irradiation were given. Eight patients underwent operation, either before or following high voltage therapy. Two patients with adenocarcinoma (cases 4 and 5) showed no improvement, from the standpoint of expansion of the fields or of acuity, following irradiation. Their vision continued to fail, and both submitted to operation. One (case 4) died following the operation, apparently from cerebral edema. The second (case 5) had an exploratory operation by Dr. Learmonth at the Mayo Clinic. A malignant condition was suspected, and a small portion of the tumor was removed. It proved to be adenocarcinoma type II, according to the Mayo classification. Later, the patient was given high voltage and radium therapy without improvement in vision. In short, there was a general failure of vision covering a period of approximately two years.<sup>20</sup>

One patient with presumed cystic adenoma (case 9) showed no improvement following high voltage therapy. His vision continued to

---

20. Some have doubted if, in fact, a true adenocarcinoma of the pituitary gland exists. It is true that different tumors vary considerably in rate of growth, and that certain of them show marked rapidity of growth, as can be seen histologically. The rapidity of growth is judged largely by the frequency of mitotic cell division. If pituitary adenomas ever become truly malignant, they apparently differ from malignant changes in other ductless glands in that they do not metastasize outside the intracranial chamber. Confusion regarding this point has occasionally arisen in the epithelial type of carcinomas arising from the nasopharynx and metastasizing not only to the submaxillary glands, but elsewhere in the body. Such instances have been reported as malignant changes in craniopharyngeal pouch tissue. We are inclined to agree with Cushing that while the pituitary adenomas show different characteristics in rate of growth and certain cell changes, it is doubtful if they should ever be classed as truly malignant. We have followed the pathologist's classification in cases 4 and 5, listing the tumors as adenocarcinoma, although we doubt their actual malignancy.

fail in spite of a fairly long course of small doses. Operation was refused. The exact pathologic process has not been determined. A similar situation was present in case 21, in which exploration revealed a cystic chromophobe adenoma, as had been anticipated following failure to respond to irradiation. The fields promptly returned to normal following the operation.

Five patients with presumed chromophil tumor (1, 13, 18, 22 and 23), all of whom had acromegalic symptoms, showed marked improvement in the visual fields following irradiation. The patient in case 1 retained improved vision for more than nine years. One acromegalic woman (case 13) showed only slight constriction of the visual fields before irradiation, the fields returning to normal in about three months and remaining so for more than two years. Her headaches were not relieved, despite a liberal subtemporal decompression and irradiation. An attempt to explore the growth in case 18 was unsuccessful, owing to great intracranial pressure. A liberal decompression was therefore provided. The patient had the most intensive irradiation of any in the series, with remarkable improvement in vision. In fact, two years later his vision was practically normal. The improvement of vision could have been attributed only to high voltage therapy and not to operation on the growth. The decompression, however, made possible the employment of more intensive radiation than could otherwise have been used. He showed no untoward reaction following the treatments, and, in addition to recovery of practically normal vision was entirely relieved of headaches. A young woman (case 22) with early but definite acromegalic tendencies, responded very well to high voltage therapy. Her fields showed more rapid improvement than any other in the series. There was moderate constitutional reaction in connection with the treatments. In case 23, a woman with advanced acromegaly showed marked improvement of the fields following high voltage therapy. In addition, her headaches practically disappeared, and a palsy of the left abducens muscle disappeared. She had been under observation for four months. As nearly as can be judged, there was no advance in the acromegalic status of any of these patients. We feel that the acromegalic patient with a chromophil tumor reacts most favorably to deep irradiation.

Twelve patients with presumed chromophobe adenoma (cases 2, 3, 6, 7, 8, 10, 11, 14, 15, 16, 17 and 20) were given high voltage therapy. Their reaction was anything but uniform. In some instances slight improvement of vision was noted for a short time; in others an unlooked for improvement occurred and was maintained. Again, not only was there no improvement, but the vision continued to fail; the tumor in the latter cases was, with few exceptions, found to be cystic at subsequent operation.

One patient (case 6), whose tumor was classed as chromophobe adenoma, showed definite signs suggesting Fröhlich's syndrome. He was a lad of 16, in whom none of the secondary sexual characteristics had developed and who was 4 feet, 11 inches tall and weighed 95 pounds. Within two years following irradiation he gained 6 inches (15 cm.) in height and 16 pounds (7 Kg.) in weight, being 5 feet, 5 inches tall and weighing 111 pounds. In addition to this, his headaches disappeared entirely and the visual fields and acuity showed marked improvement. He has done well in school. A woman of 32 (case 7), with amenorrhea, showed marked improvement in acuity and definite enlargement of the visual fields, which was maintained for more than three years, but there was no return of menstrual function. The visual fields, consisting of a temporal hemianopia on the right and an island of vision in the upper nasal field on the left, remained practically stationary during this period. While irradiation did not improve the fields as much as could be desired, it apparently held them at a higher level than would otherwise have been the case. An exploratory operation on the gland may be necessary. Another woman (case 8) with a proved chromophobe adenoma, as shown by operation following irradiation, did not improve as much as one would wish. She was operated on approximately six weeks after the last course of irradiation. A fibrous type of chromophobe adenoma was found and partially removed. The wound healed by first intention, but after about ten days broke down in several places, which required several weeks to heal. The only patient (case 14) who came to autopsy following irradiation was a man of 68, with a chromophobe adenoma. He showed marked improvement in the fields and acuity following high voltage therapy. His death, some eighteen months later, was due to apoplexy. On histologic study, the pituitary gland showed a chromophobe adenoma, and the pathologist felt that it showed no increase in fibrosis or other cellular change as a result of the treatment. In short, no appreciable change as a result of irradiation was noted.

It had been the impression of one of us (C. W. R.) that fibrous changes in the tumors followed irradiation, making a subsequent surgical procedure less effective. However, one patient (case 21), with a proved chromophobe adenoma, came to operation within six days of very active high voltage therapy. This became necessary because of rapidly failing vision. A cystic chromophobe adenoma was encountered and partially removed. Because of the recent irradiation, it was expected that the tissues would react unfavorably at operation. This was not the case. There was no increase of bleeding, and the wound healed quickly by first intention.

#### COMMENT ON ROENTGEN THERAPY

The treatments were practically all given, except as otherwise noted, with constant factors of 186 kilovolts, a 0.75 mm. copper and a 1 mm.

aluminum filter, and a distance of 50 cm. from the skin to the target, through ports 2 inches (5 cm.) square. The factors used in the patients treated elsewhere were supposedly the same as ours. However, in some the actual amount and quality of radiation received are problematic.

In carrying out the treatments, multiple ports were used. It seemed practical to use two lateral, one anterior or frontal and one occipital, and if desired, one through the vertex, limiting their size with a lead apron or suitable cone. By rotating the treatments properly through the various areas, an opportunity for cross-firing and the delivery of considerable total radiation at the site of the tumor is possible. This can be accomplished without much danger to the hair or skin. We have had a few cases of transient epilation. These followed the earlier treatments, when proper rotation of the ports of entry was not observed. Epilation was seldom seen in the temporal areas, but more often in the frontal and occipital.

The distance from the skin to the pituitary gland through the different ports results, of course, in a varying dose being delivered to the tumor. The temporal areas, being nearest to the tumor, are the most efficient to use. Depending on the diameter of the individual patient's head, it is possible to deliver from 45 to 55 per cent of the dose at the skin to the tumor through each temporal port, from 35 to 45 per cent through the frontal and from 25 to 30 per cent through the occipital and vertex ports. The individual doses delivered to the tumor varied from 7 to 25 per cent of a skin erythema dose. The treatments were generally given on each alternate day, with 200 r on the skin as measured in air. If after a few treatments there was increased blurring of vision or if headaches resulted or increased in severity, the treatments were reduced to 150 r each, or a treatment or two was omitted. Occasionally, a patient was found who tolerated treatment exceptionally well and 150 or even 200 r could be given daily.

Two factors in connection with the treatment probably have a definite influence on the outcome: first, the sensitivity of the tumor to irradiation, and, second, the ability of the patient to take treatment in sufficient amount and rapidly to get effective dosage at the tumor. There seems to be no doubt that a previously performed decompression allows the delivery of more rapid and complete dosage to the pituitary gland without causing disagreeable after-effects. It is obvious that doses varying from 7 to 25 per cent, unless frequently and consistently given, will not deliver sufficient irradiation to have much influence on even the most sensitive tumor.

The patients in this series were practically all outpatients and under poor control. Some occasionally failed to keep their appointments, and the regularity of the dosage was therefore interrupted, so that the



depreciation effect was sometimes nearly as great as the subsequent dose; hence, accumulation might be practically at a standstill.

Owing to the rather alarming reaction shown by the first patient, to whom 200 and 300 r doses were given, treatment for subsequent patients was in the form of smaller doses given frequently and rapidly in an attempt to build up a saturation of satisfactory degree at the tumor. Either on account of the interval between treatments or the noncooperation of the patient, it may be impossible to build up a satisfactory dose at the tumor by this method. The results, perhaps, in this series would have been more satisfactory if it had been possible always to obtain a saturation dose. This could be accomplished only by having the patient under perfect control.

Irradiation, if at all intensive, probably causes a definite but varying degree of swelling and edema in the irradiated tissue. We believe that there may be an increase in the local pressure when this takes place inside an unopened skull. It might easily be shown in an accentuation of such symptoms as are due to increased pressure, especially headache, increased blurring of vision, nausea and vomiting.

#### SUMMARY AND IMPRESSIONS

An attempt has been made in a study of twenty-three cases to estimate the value of high voltage irradiation in the treatment of various types of tumors of the pituitary gland. The types analyzed have included: chromophil adenoma (five cases), chromophobe adenoma (thirteen cases), adenocarcinoma (two cases) and cystic chromophobe adenoma (three cases). The various types of tumors react differently. The problem as to the value of irradiation is far from solved, and at the present time a definite answer cannot be given.

Chromophil adenomas react most favorably to this form of treatment. The permanency of relief is indefinite. Cases have been cited in which visual improvement has been maintained from four months to nine years following high voltage therapy. One case, not included in the series, but one which came to the attention of one of us, showed improvement for ten years. While we have no case of basophilic adenoma to include in this group, reports which have begun to come in would seem to indicate that this type of tumor also reacts favorably to high voltage irradiation. Some believe that eosinophilic and basophilic cells are of a higher type than the indifferent chromophobe or chief cells. They should, theoretically, be more resistant to irradiation. On the contrary, they apparently react most favorably to this form of treatment.

Chromophobe adenomas have not responded uniformly to irradiation. This has been difficult to explain. It may be partly due to the fact that their treatment has not been uniform. In some cases the dosage

was insufficient and the course of irradiation incomplete. If the chromophobe cells, as some contend, are more embryonic than eosinophilic or basophilic cells, one would expect better results from irradiation. It must also be borne in mind that tumors of the pituitary gland do not necessarily run true to type, but may, to some degree, be mixed. The predominating cells may be of the chromophobe type, but there may also be present a smattering of other types of cells.

Adenocarcinoma of the pituitary gland apparently does not react favorably to high voltage irradiation. In view of the fact that mitosis of the cells is frequent one might expect that they would be more sensitive to irradiation. This does not appear to be true. There is a question whether, in fact, these tumors should be considered as true carcinomas; at all events, they do not metastasize extracranially.

Cystic adenomas of the chromophobe variety show no improvement following irradiation. This has been observed by others, and from the very nature of the growth is to be expected. Some of the tumors may be solid at first, later becoming cystic. It seems to us not unreasonable that, taken in conjunction with the clinical findings, a fairly accurate differential diagnosis between a cystic and a noncystic tumor can be made. This is judged largely by their reaction to high voltage irradiation. When apparent chromophobe tumors fail to react favorably to irradiation within a short time they are very likely cystic and more amenable to surgical treatment.

We are unprepared to state what, if any, morphologic changes in the gland can be demonstrated subsequent to high voltage irradiation. No demonstrable changes were seen in one case of chromophobe adenoma of this series which came to autopsy. However, the material was not obtained until a year after irradiation had ceased, and earlier demonstrable changes might easily have been missed.

Irradiation can be given more intensively if a decompression is first provided.

Apparently certain patients suffering from pituitary tumors gain from moderate to useful vision following irradiation. In some the gain may be held and the vision remain stationary for years. Without irradiation they would almost certainly become blind.

We have seen no definite regression in general acromegalic symptoms following irradiation. On the other hand, we have not seen any definite advance in symptoms. This point can be more definitely decided after a longer period of years has elapsed.

The literature contains many reports of brilliant results in changes in the fields immediately following partial surgical removal of tumors of the pituitary gland. Late results, however, are seldom given, so that it is more or less of a conjecture how long the improvement in vision may have lasted. In our experience, postoperatively, patients

without irradiation have maintained improved vision on an average of from one to three years. In various clinics, surgical intervention followed by high voltage irradiation is more or less a routine. It would not seem illogical in selected cases to employ irradiation first, in the hope that certain patients may be helped enough thereby to render surgical intervention unnecessary.

It should again be strongly emphasized that these cases should at all times be under the close scrutiny of a neurologic surgeon, who closely follows changes in the eyegrounds and fields, and who will frequently be called on to perform an operation. For at best, high voltage irradiation will give satisfactory results in only a certain percentage of cases. It does not replace surgical procedure, but rather acts as an adjunct to it.

# EFFECT OF SUPRARENAL DENERVATION AND SPLANCHNIC SECTION ON THE SUGAR TOLERANCE OF DOGS

GÉZA DE TAKÁTS, M.D.

AND

FLORIAN P. CUTHBERT, B.S.

CHICAGO

In a previous study<sup>1</sup> we found that the removal of the celiac ganglion resulted in a decided, persistent rise of tolerance in every instance. The dogs became more sensitive to insulin. A denervation of the liver did not produce a rise in tolerance. To analyze the mechanism of our previous results, the rôle of the suprarenal glands was investigated in the study to be reported here.

Elsewhere<sup>2</sup> we summarized the literature on the effect of suprarenal denervation and of splanchnic section on sensitivity to insulin. It was reported uniformly that removal of the medulla, denervation of suprarenal glands or bilateral splanchnic section renders the animals more sensitive to insulin. The determination of hypersensitivity to insulin was only roughly quantitative, the criterion being whether convulsion occurred with a dose of insulin which prior to the operative procedure failed to cause convulsion. Regarding sugar tolerance before and after suprarenal denervation or splanchnic section, the only data available were found in a communication by Banting and Gairns,<sup>3</sup> who stated that twenty-four hours after double suprarenalectomy 2 Gm. of dextrose per kilogram given intravenously produced the same blood sugar curve as before operation. Finally, Ciminata<sup>4</sup> claimed, on the basis of a single experiment, that suprarenal denervation protects a pancreatectomized dog from diabetes. Critical collective reviews on

---

From the Department of Physiology and Pharmacology, Northwestern University Medical School.

1. de Takáts, G., and Cuthbert, F. P.: The Effect of Coeliac Ganglionectomy on the Sugar Tolerance of Dogs, *Am. J. Physiol.* **102**:615, 1932.

2. de Takáts, G., and Cuthbert, F. P.: Surgical Attempts at Increasing Sugar Tolerance, *Arch. Surg.* **26**:750 (May) 1933.

3. Banting, F. G., and Gairns, S.: Suprarenal Insufficiency, *Am. J. Physiol.* **77**:100, 1926.

4. Ciminata, A.: Einfluss der Durchschneidung der Nebennieren auf den Diabetes Mellitus, *Klin. Wchnschr.* **11**:150, 1932.

the physiology of the suprarenal glands were published by Bayer<sup>5</sup> and Britton.<sup>6</sup>

In this study our previously described methods of determining tolerance for sugar<sup>7</sup> and sensitivity to insulin<sup>1</sup> were applied to the study of the effect of bilateral suprarenal denervation. Bilateral section of the splanchnic nerves was scrutinized in the same manner.

#### METHODS OF EXPERIMENTATION

The tolerance to an intravenous injection of an isotonic dextrose solution at timed rates is a constant and repeatedly checked amount of dextrose that can be injected during an hour without producing glycosuria. It is never above 1.9 Gm. of dextrose per kilogram of body weight in the normal, well relaxed dog.<sup>8</sup> Following the operation repeated determinations of tolerance were made at monthly intervals. The dogs were observed for from six months to a year and a half and were finally killed to obtain histologic sections of the liver, suprarenal glands and pancreas. The sensitivity to insulin was determined by giving one-tenth unit per kilogram of body weight in 1 cc. of physiologic solution of sodium chloride. The blood sugar was determined before, and ten, twenty and thirty minutes and one hour and two hours after, the injection. Some observations were also made on the epinephrine hyperglycemia before and after operation, 0.02 mg. of epinephrine per kilogram of body weight being injected intravenously. Finally, the effect of double supradiaphragmatic vagotomy on the rise in tolerance obtained by splanchnic section was studied.

The technic of suprarenal denervation was as follows: An abdominal incision was made parallel to the right costal arch. The right suprarenal gland was exposed lateral to the vena cava. Between the diaphragm and the suprarenal gland, in the loose retroperitoneal tissue, the right major splanchnic nerve was picked up with a hook and dissected cephalad as far as possible, and a segment 1 inch (2.5 cm.) long was excised. The regeneration of this nerve takes place rapidly in the dog. A search was also made for the minor splanchnic filaments, which lie in a slightly deeper plane. Next, the large suprarenal plexus, which lies between the suprarenal and the celiac ganglion, was dissected out and severed; thus all of the nervous connections of the gland were interrupted. The same procedure was repeated on the left side, where, because of the absence of the liver and the vena cava, the dissection is much easier. In earlier experiments, a right suprarenalectomy was done, and the left suprarenal gland was denervated.

For bilateral splanchnic section, the right and left major and minor splanchnic nerves were excised, but the suprarenal plexus was not disturbed. The splanchnic nerves were also exposed in one dog above the diaphragm, in the posterior medias-

5. Bayer, G.: *Handbuch der inneren Sekretion*, Leipzig, Curt Kabitzsch, 1927, vol. 2, p. 641.

6. Britton, S. W.: *Adrenal Insufficiency and Related Considerations*, *Physiol. Rev.* **10**:617, 1930.

7. de Takáts, G.; Hannett, F.; Henderson, D., and Seitz, I. J.: The Effect of Isolating the Tail of the Pancreas on Carbohydrate Metabolism, Correlation of Internal and External Pancreatic Secretion; *Arch. Surg.* **20**:866 (May) 1930.

8. Determinations of tolerance carried out by several workers in this laboratory in over fifty normal dogs yielded an average of 1.87 Gm. of dextrose per kilogram of body weight per hour.

tinum, but this approach offered no advantages in the dog. Double supra-diaphragmatic vagotomy was performed through an incision in the eighth or ninth intercostal space. The pleural cavity was rapidly opened, the esophagus was picked up and the two vagus nerves were cut to the right and to the left of the esophagus. The resulting pneumothorax was quickly expressed, and the pleural gap was sutured rapidly in maximal expiration, with two heavy sutures approximating the two neighboring ribs. The intrapleural part of the operation usually did not take more than a minute or two. The intestinal muscles and skin were carefully sutured.

TABLE 1.—*Rise in Sugar Tolerance Following Suprarenal Denervation*

Dog	Preoperative Tolerance,* Gm. per Kg. per Hour	Postoperative Tolerance,† Gm. per Kg. per Hour	Rise, per Cent
69.....	1.8	3.35	80.6
70.....	1.84	2.92	58.6
79.....	1.8	2.85	58.3
82.....	1.8	2.94	63.3
83.....	1.87*	2.92	62.22
84.....	1.87*	2.82	56.66
89.....	1.87*	2.96	64.44
90.....	1.8	2.78	54.44
91.....	1.8	3.00	66.66
93.....	1.87*	3.00	66.66
95.....	1.87*	2.91	61.66
96.....	1.87*	2.57	42.77
Average.....	1.84	2.94	61.36

\* Determinations of tolerance on over fifty normal dogs gave figures of 1.87 Gm. of dextrose per kilogram per hour. In these dogs the preoperative tolerance was not determined.  
† Average of several determinations.

TABLE 2.—*Sensitivity to Insulin Following Suprarenal Denervation*

Dog	Post-operative Period, Weeks	During Fasting	Blood Sugar, Mg. per 100 Cc.				
			Minutes After Injection of Insulin				
			10	20	30	60	120
70	10	74.2	55.2	37.4	39.0	46.7	68.7
79	12	88.5	69.5	31.4	31.2	31.2	62.5
82	11	99.0	86.2	55.6	45.1	51.3	99.0
83	8	84.7	68.0	42.7	40.2	49.5	74.6
84	9	75.8	52.3	34.9	41.3	43.7	76.9
89	3	73.0	62.9	52.3	45.7	46.3	70.4
Average.....		82.5	65.7	42.4	39.6	44.8	75.3

## RESULTS

The rise in sugar tolerance following suprarenal denervation is shown in table 1. The average rise in twelve experiments was 61.36 per cent of the preoperative level, and the rise varied from the maximum of 3.35 Gm. of dextrose per kilogram per hour to the minimum of 2.57 Gm. per kilogram per hour. As in the previous series of dogs subjected to celiac ganglionectomy, the maximal rise in tolerance was obtained after the animal had recovered from the operation and was maintained indefinitely unless an infection or intestinal complication developed. Intestinal complications will be discussed later.

The response of these dogs to insulin was definitely increased. The blood sugar curves are shown in table 2. Determinations were made between three weeks and eleven weeks after operation. A composite graph (chart 1) comparing the susceptibility to insulin of normal dogs with that of dogs which underwent celiac ganglionectomy, suprarenal denervation, splanchnic section and splanchnic section with added bilat-

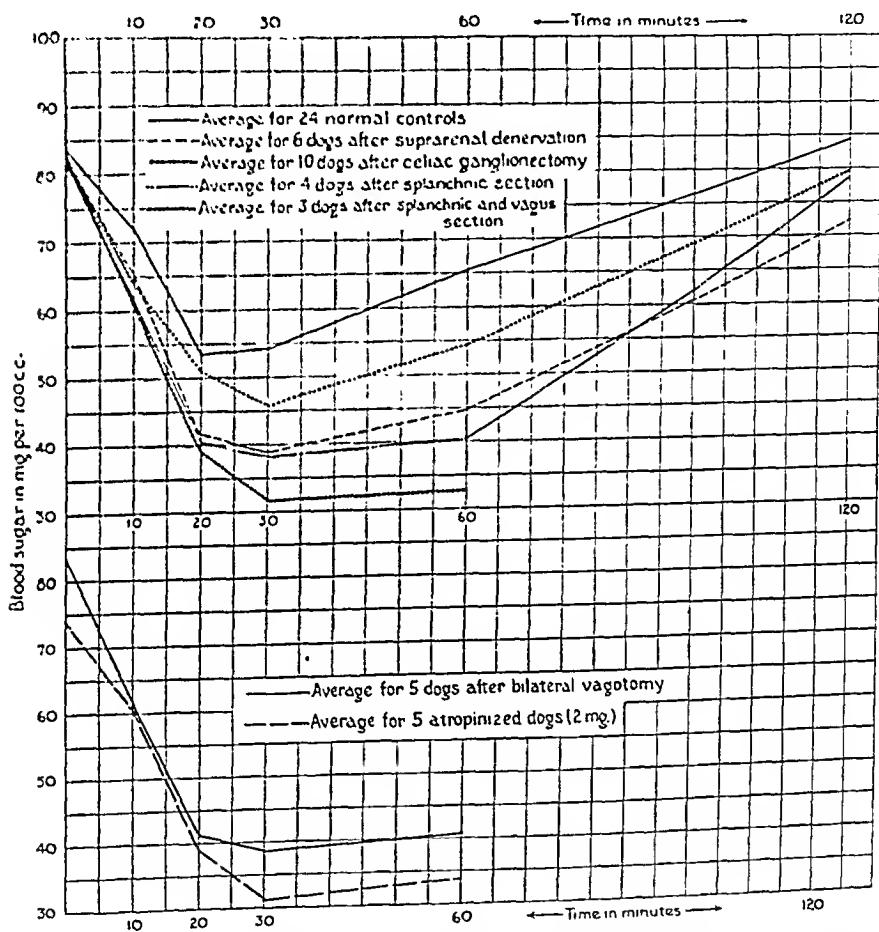


Chart 1.—Curves showing the sensitivity to insulin, as indicated by the blood sugar. One-tenth unit of insulin was given intravenously in 1 cc. of physiologic solution of sodium chloride. The blood sugar was determined by the modified Folin-Wu method, before the administration of insulin and ten, twenty, thirty, sixty and one hundred and twenty minutes afterward. Note that celiac ganglionectomy, suprarenal denervation and splanchnic section produce an increase in the sensitivity to insulin. The average of twenty-four curves for normal controls is low, because some of the determinations were made during excessive heat in the summer, and high temperatures increase the response to insulin (Krogh's, Trevan's and our observations). Following the operative procedures, the effect of heat is not noticeable on the sensitivity to insulin. Note also that bilateral vagotomy or atropinization does not diminish or abolish the reaction to insulin, as claimed by Babkin; on the contrary, it increases the sensitivity.

eral vagotomy reveals that the four groups of operations resulted in a definite enhancement of the action of insulin on blood sugar curves.

The rise in sugar tolerance following bilateral splanchnic section closely parallels that seen after suprarenal denervation (table 3). The sensitivity to insulin has also increased (table 4). The average figures check closely with those seen in table 2.

The responses to epinephrine of dogs in which suprarenal denervation was done was identical to that of dogs in which splanchnic section was done, so that the results for both experiments are shown in one table (table 5). A comparison with the figures obtained for dogs pre-

TABLE 3.—*Rise in Sugar Tolerance Following Bilateral Splanchnic Section*

Dog	Preoperative Tolerance, Gm. per Kg. per Hour	Postoperative Tolerance, Gm. per Kg. per Hour	Rise, per Cent
64.....	1.9	2.81	47.8
100.....	1.8	2.90	61.1
102.....	1.8	2.89	60.5
103.....	1.8	2.79	55.5
105.....	1.8	2.73	51.8
106.....	1.8	2.88	60.6
97.....	1.8	3.45	91.6
98.....	1.8	2.74	52.2
104.....	1.8	2.61	45.0
Average.....	1.8	2.86	58.8

TABLE 4.—*Sensitivity to Insulin\* After Bilateral Splanchnic Section*

During Fasting	Minutes After Injection of Insulin				
	10	20	30	60	120
86.2	55.2	49.6	51.8	52.2	85.5
69.5	41.0	27.2	25.1	23.1	....
88.5	69.5	31.4	31.2	25.3	62.5
99.0	86.2	55.6	45.1	51.3	99.0
85.8	63.0	40.95	38.3	41.2	82.3

\* The figures represent milligrams of sugar per hundred cubic centimeters of blood.

vious to operation (table 6) indicates that these operations definitely depress, although they do not entirely suppress, hyperglycemia due to epinephrine. In chart 2 the upper two curves illustrate the effect of splanchnic section on epinephrine hyperglycemia, the dose of 0.02 mg. of epinephrine per kilogram of body weight having been given. The middle two curves show the effect of suprarenal denervation on the response to epinephrine which is equally definite, but the smaller dose of 0.01 mg. per kilogram was given intravenously. The lower curves represent the average for seven normal animals and eight animals on which operation had been performed. The dose was 0.02 mg. per kilogram of body weight. The blood sugar during fasting is



lower and the peak of the rise, which appears between five and ten minutes after the injection, is lower in the group with suprarenal denervation.

When supradiaphragmatic double vagotomy was added to bilateral splanchnic section, the tolerance did not change except in one instance,

TABLE 5.—*Response of the Blood Sugar\* to Epinephrine in Dogs with Suprarenal Denervation or Splanchnic Section*

During Fasting	Minutes After Administration of Epinephrine				
	10	20	30	60	120
95.2	104.8	96.6	95.2	89.7	84.4
96.0	98.7	97.3	95.6	89.3	71.2
83.3	101.0	97.6	75.2	76.1	81.6
71.3	84.4	70.7	70.8	74.7	71.7
83.0	94.3	81.6	81.3	74.9	70.0
80.3	91.0	81.3	75.6	78.3	79.1
72.7	80.6	80.8	64.4	69.3	71.8
81.0	91.3	93.0	90.1	88.1	84.0
79.2	89.0	83.5	76.0	76.3	76.9

\* The figures represent milligrams of sugar per hundred cubic centimeters of blood.

TABLE 6.—*Hyperglycemia\* Due to Epinephrine in the Normal Dog*

During Fasting	Minutes After Administration of Epinephrine				
	10	20	30	60	120
100.5	122.7	117.6	107.0	98.6	85.9
103.3	154.7	160.6	137.2	127.1	99.4
108.7	122.0	137.0	122.7	119.0	111.7
102.1	87.8	93.9	97.6	88.9	88.5
85.1	119.0	92.7	90.5	....	87.4
86.6	114.3	99.0	87.4	86.2	....
102.1	110.5	98.6	97.1	100.5	103.4
98.6	118.7	114.2	105.6	103.4	96.05

\* The figures represent milligrams of sugar per hundred cubic centimeters of blood.

TABLE 7.—*The Effect of Double Vagotomy on the Rise in Sugar Tolerance Obtained After Bilateral Splanchnic Section*

Dog	Sugar Tolerance*	
	Before Vagotomy	After Vagotomy
102.....	2.73	2.73
97.....	3.45	3.19
98.....	2.74	2.61

\* Expressed in grams per kilogram per hour.

but here the determination was done too soon after the operation (table 7). Nor did vagotomy change the increased sensitivity to insulin obtained after splanchnic section; if anything, it slightly increased it. Doses of atropine of from 2 to 2.5 mg. given before the administration of 5 units of insulin intravenously did not diminish the action of the insulin and the blood sugar values showed a close similarity to those obtained after double vagotomy (chart 1, lower two curves).

# OTHER OBSERVATIONS

The surgical mortality was very low, but some animals were so listless and adynamic after the suprarenal denervation that they were given ephedrine in doses of 15 mg. twice a day for the first day or two after

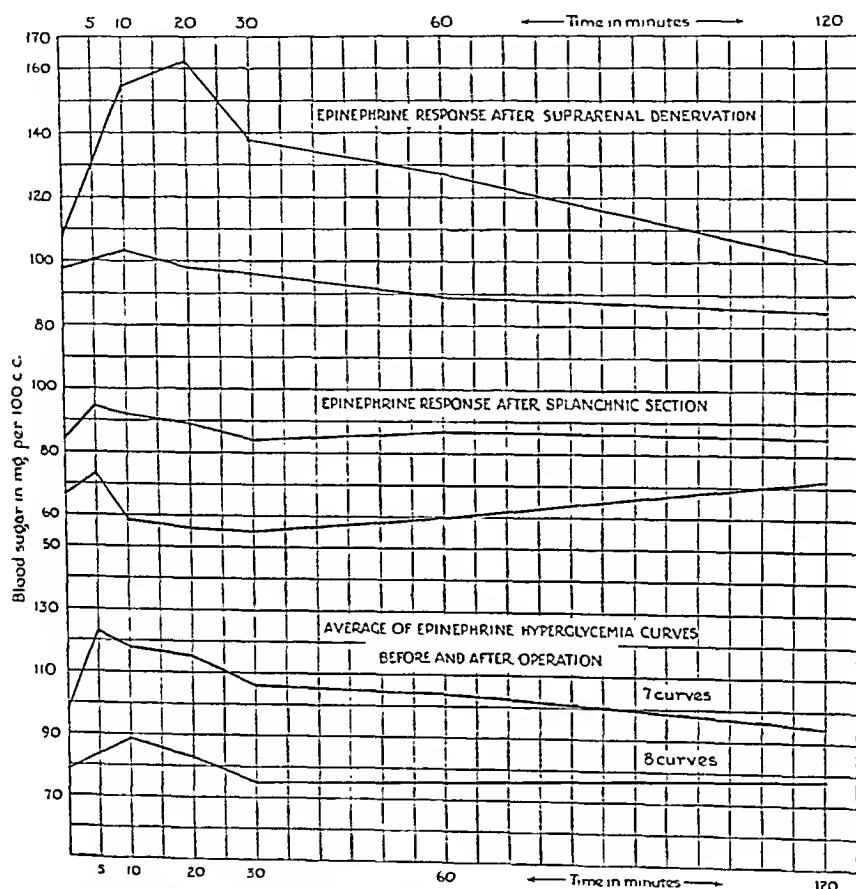


Chart 2.—Curves showing hyperglycemia due to epinephrine. Epinephrine was given intravenously in doses of 0.02 mg. in 1 cc. of physiologic solution of sodium chloride. Tests for blood sugar were made before the injection and five, ten, twenty, thirty, sixty and one hundred and twenty minutes afterward. The upper and middle pairs of curves, showing the response following suprarenal denervation and splanchnic section, respectively, represent single experiments before and after operation, while the lowest two curves represent averages after both types of operation. In the three groups the upper curve is preoperative, and the lower curve postoperative. Note that the blood sugar during fasting is lower after suprarenal denervation or splanchnic section. The rise of the blood sugar curve is less pronounced after these two operations, or may even be inverted in individual curves (not shown in this graph). The curves indicate that glycogen is more difficult to mobilize after the operation, provided the glycogen content of the liver is not diminished. Our unpublished data indicate that there is a rise of glycogen in the liver after splanchnic section.

the operation. About one third of the animals had postoperative diarrhea, but this was readily controlled by atropine.

All of the dogs studied in the series were killed, and autopsies were performed at the conclusion of the experiment. The cut ends of the splanchnic nerves were found matted together in a neuroma in most of the earlier cases. We have since removed larger segments and believe that a regeneration of the splanchnic nerve can hardly be prevented, unless the proximal stump is implanted into a peripheral nerve.<sup>9</sup> Sections of the liver, pancreas and suprarenal glands were taken as a routine, and only a brief summary of the observations will be presented here.

The liver macroscopically looked normal. The surface was smooth, and the color and consistency were normal. On histologic section, however, the liver cells seemed large; the protoplasm was light and slightly granular and the nucleus was often pushed to one side. This change was particularly obvious around the central vein. Whether these observations mean an abnormally high deposit of glycogen is now being studied.<sup>10</sup> Preliminary staining for fat with sudan III did not reveal an unusual amount of lipoid substance. There was no increase in connective tissue. The small bile ducts and the portal and the hepatic venules were generally dilated. The entire liver was hyperemic. In dog 94, all of the smallest vessels were dilated and filled with blood.

The pancreas seemed to be more firm than is normal and was granular in consistency in some of the animals. Its color and size were normal. On section, there was an unmistakable increase in vascularity. Not only the vessels but the ducts were wide open. The acini and small ducts were filled with secretion. The size and number of islands were not studied numerically in serial sections; in certain slides, however, there was an unusual hyperemia of the islets, which enabled us to visualize the complicated vascular network.

The denervated suprarenal glands seemed of normal size and consistency, although in two of the fifteen animals studied the glands were small and atrophic. The medullary veins were gaping, and the chromaffin substance stained well. The cortex was loaded with lipoid substance and showed mitotic activity between the zona glomerulosa and the zona fasciculata. The cortical veins were not so dilated as the medullary ones. The general impression was that of increased fat storage in the cortex, the medulla being unchanged except for the venous hyperemia.<sup>11</sup>

9. Dr. S. W. Ransom made this suggestion.

10. von Gierke, E.: Hepato-Nephromegalia glycogenica, Beitr. z. path. Anat. u. z. allg. Path. 82:497, 1929.

11. Dr. R. A. Jaffé, pathologist of the University of Illinois and of the Cook County Hospital, looked over these slides.

## COMMENT

When the rise in intravenous sugar tolerance following suprarenal denervation and splanchnic section and our previously reported results following celiac ganglionectomy are compared, it will be seen that they are practically identical. Certain breeds of dogs, such as airdales, respond with higher rises in tolerance than others, but an average rise to from 2.8 to 2.9 Gm. of dextrose per kilogram per hour was obtained in all three groups of experiments. The susceptibility to insulin is also markedly exaggerated. We are aware of the many factors that influence the response to insulin, such as seasonal and atmospheric variations, previous nutrition, dehydration and temperature; nevertheless, the severance of the sympathetic innervation to the triad of liver, pancreas and suprarenal glands makes the animal unmistakably sensitive to insulin. The curves showing the response to epinephrine, on the other hand, indicate that sugar is mobilized with more difficulty from the liver, assuming, of course, that there is enough glycogen available for mobilization.

The influence of double vagotomy on the rise in sugar tolerance following suprarenal denervation or splanchnic section was found to be negligible. Quigley and his co-workers have found<sup>12</sup> that secretion of insulin following hyperglycemia is at least as active with both vagus nerves cut as in the normal animal. The rises in tolerance which we noted, therefore, do not seem to be explained on the basis of a vagosympathetic imbalance. While we have previously reported that denervation of the liver alone did not seem to produce a rise in tolerance or an increased sensitivity to insulin, there are uniform histologic changes in the liver and the portal system that require further study. The liver cell is loaded with a substance, and if this proves to be glycogen, the changed responses to insulin and epinephrine might be explained by a "glykopexy," or increased glycogen fixation.

The effect of splanchnic section on the suprarenal medulla has been studied by a large number of workers.<sup>5</sup> Important is the work of Hoshi,<sup>13</sup> who observed disappearance of nerve fibrils in the medulla within from four to eight days after splanchnic section. Section of the vagus has no effect on the microscopic picture. Hoshi stated the belief that there are no ganglions in the medulla and no synapsis in the celiac ganglion, which would mean that both splanchnic section and celiac ganglionectomy would be postganglionic neurotomies.

12. Quigley, J. P.; Halloran, W. R., and Barnes, B. O.: Variations in Blood Sugar Values of Normal and Vagotomized Dogs Following Glucose Administration, *J. Nutrition* 5:77, 1932.

13. Hoshi, T.: Morphologisch-experimentelle Untersuchungen über die Innervation der Nebennieren, *Mitt. d. allg. Path. u. path. Anat.* 3:328, 1927.

That hypoglycemia due to insulin stimulates medullasuprarenal secretion has been sufficiently emphasized by Cannon.<sup>14</sup> Kahn<sup>15</sup> showed that histologic changes occur in the medulla of the suprarenal glands and also in the aortic paraganglion following the administration of insulin, but that this can be effectively prevented by splanchnic section.

Raab<sup>16</sup> expressed the belief that epinephrine is the direct antagonist of insulin so far as glycogen fixation in the liver is concerned. If one inhibits the secretion of epinephrine that follows the administration of insulin by splanchnic section, an increased glycogen fixation should result.

The work of Kutschera-Aichbergen<sup>17</sup> deserves to be mentioned in connection with our work. He believed that he had shown that, while epinephrine usually flows through the central vein to the vena cava, the vein, which is unusually muscular, may be closed by spasm; the result is the shunting of the epinephrine through the cortical veins and into the portal system, whence it acts more directly on the glycogen. Kutschera-Aichbergen explained piqure glycosuria by such a spasm of the central vein. Splanchnic section may abolish such central impulses to the central vein, and it has been repeatedly shown that no central hyperglycemia can be produced after section of the splanchnic nerve (Mock and de Takáts<sup>18</sup>).

The rôle of the suprarenal cortex in carbohydrate metabolism has been recently discussed by Britton and Silvette<sup>19</sup> and Silvette.<sup>20</sup> According to these investigators, corticosuprarenal extract increases the rate of glycolysis in vitro, raises the liver glycogen and increases the blood sugar in the animal suffering from cortical insufficiency. The observations of Tokomitsu<sup>21</sup> are interesting; he stated that following ligation of the pancreatic duct in the rabbit, the suprarenal cortex enlarges from one and one-half to two times its original size and many mitoses are seen at

14. Cannon, W. B.; McIver, M. A., and Bliss, S. W.: A Sympathetic and Adrenal Mechanism for Mobilizing Sugar in Hypoglycemia, *Am. J. Physiol.* **69**: 46, 1924.

15. Kahn, R. H.: Ueber die zentrale Reizung der Nebennieren und der Paraganglion während der Insulinvergiftung, *Arch. f. d. ges. Physiol.* **212**:54, 1926.

16. Raab, W.: Glykogen-Fixation mit Insulin, *Klin. Wchnschr.* **3**:1678 (Sept. 9) 1924.

17. Kutschera-Aichbergen, H.: Nebennieren Studien, Frankfurt. *Ztschr. f. Path.* **28**:262, 1922.

18. Mock, H., and de Takáts, G.: Hyperglycemia Following Head Injuries, *Ann. Surg.* **90**:190, 1929.

19. Britton, S. W., and Silvette, H.: The Apparent Prepotent Function of the Adrenal Glands, *Am. J. Physiol.* **100**:701, 1931.

20. Silvette, H.: Effects of Cortico-Adrenal Extract on Glycolysis in Vitro, *Am. J. Physiol.* **102**:693, 1932.

21. Tokomitsu, Y.: Ueber eine neue Funktion der Nebennierenrinde, *Mitt. u. allg. Path. u. path. Anat.* **1**:161, 1921.

the zona spongiosa. He thought that the cortex and the pancreatic islets are synergists, and that a compensatory cortical hypertrophy prevents the animals from becoming diabetic. When the cortex was removed, glycosuria of long duration developed. The report of a case of diabetes in which the patient, who died in coma, was resistant to insulin, was published by Chiari;<sup>22</sup> a marked hypertrophy of the cortical cells was found in a true cortical adenoma. In a previous communication<sup>2</sup> we reported cortical enlargement following ligation of the tail of the pancreas.

What suprarenal denervation or splanchnic section does to cortical secretion, particularly in regard to carbohydrate metabolism has not been studied so far. Our histologic observations indicate that there is an increased storage of fat. Cortical atrophy is known to occur after hypophysectomy. Cortical hypertrophy can be induced by the adrenotropic hormone of the anterior pituitary gland, and this may be one of the links between carbohydrate metabolism and the pituitary gland.

#### SUMMARY

Suprarenal denervation and section of the splanchnic nerve are equally effective in raising the sugar tolerance of normal dogs. Thus the previously reported effect of celiac ganglionectomy can be explained by its denervating effect on the suprarenal glands. The dogs are more responsive to insulin and less responsive to the hyperglycemic action of epinephrine. Bilateral vagotomy does not diminish the rise in sugar tolerance obtained by these operations. These data add to the knowledge of the stimulating effect of the sympathicosuprarenal system on the mobilization of glycogen. The interruption of this mechanism may lead to increased glycogen storage or fixation of glycogen in the liver.

NOTE.—Since this article went to press, it has been definitely established that splanchnic section produces an increased storage and also an increased fixation of glycogen.

---

22. Chiari, H.: Ein Fall von Diabetes mit Hypertrophie der Nebennieren-Rinde, *Wien. klin. Wchnschr.* 42:1318, 1929.

# GASTRIC SECRETION

## V. ACHILORHYDRIA FOLLOWING PARTIAL GASTRECTOMY FOR ULCER: STUDIES WITH HISTAMINE AND THE TRANSPLANTED GASTRIC POUCH

EUGENE KLEIN, M.D.†

NEW YORK

The operation of partial gastrectomy has furnished an opportunity for the study of many of the problems of gastric physiology. The present paper is not primarily concerned with the results following this procedure. These have recently been discussed by Berg,<sup>1</sup> who introduced the operation in this country as the procedure of choice in the treatment of gastric and duodenal ulcer. But in spite of the numerous advances in physiology and their evident bearing on the subject, there still exists an apparent misunderstanding of the mechanisms involved. Since considerations of function are at least as important as those of structure, it may not be amiss to emphasize again the underlying facts and at the same time add some clarifying experiments.

The first point to grasp is that the gastric secretion following a meal is not a single response to one type of stimulus. It is the total of responses to at least three, and probably more, entirely separate groups of stimuli. Further, the mechanisms of these groups vary considerably. It is possible to influence one without affecting the others.

Briefly considered, the three chief phases are (1) primary (psychic, cephalic); (2) secondary (gastric, chemical), and (3) intestinal.

(1) The primary phase is reflex, and the reflex pathway reaches the stomach over the vagus system. Seeing or smelling food may initiate the stimulus and tasting, chewing and swallowing continue it. The secretion starts about five minutes after the beginning of the sensory stimulation and persists for about two hours after it ceases. The secretion varies in amount, being more profuse during hunger than after the appetite is appeased. Section of the vagi suppresses this secretion.<sup>2</sup>

---

† Dr. Klein died on Oct. 2, 1932.

From the Service of Dr. A. A. Berg and the Department of Laboratories, Mount Sinai Hospital.

1. Berg, A. A.: The Radical Operative Cure of Gastric and Duodenal Ulcer, *S. Clin. North America* 8:1167, 1928; The Mortality and Late Results of Sub-total Gastrectomy for the Radical Cure of Gastric and Duodenal Ulcer, *Ann. Surg.* 91:340, 1930.

2. (a) Uschakow: *Dissert.* St. Petersburg, p. 20; quoted by Babkin, B. P.: *Die äussere Sekretion der Verdauungsdrüsen*, Berlin, Julius Springer, 1928, p. 398. (b) Pavlov, I. P.: *The Work of the Digestive Glands*, ed. 2, London, C. Griffin & Company, 1910.

(2) The secondary or chemical phase begins after the entrance of food into the stomach. It is due to chemical substances in the food. These do not directly stimulate the secretory cells. There are no acid cells in the antrum or distal portion of the stomach. They are all situated in the body and fundus. But it is through the antrum that the chemical stimuli act.<sup>3</sup> This fact is physiologically well established, but clinically is not so well known. The mechanism is only partly understood. The chemicals from the food (secretagogues) either are directly absorbed into the blood stream or produce a hormone in the antrum which is absorbed and carried to the secretory cells through the blood. It is the antrum or the site of the chemical stimulation that is removed by the operation of partial gastrectomy.

(3) The intestinal stimulus is not so well understood as the others. It apparently starts late after a meal (from one to six hours) and accounts for only a small part of the secretion.<sup>4</sup>

In addition to those clearly defined phases, there is the spontaneous secretion. This seems to be due chiefly to conditioned reflexes reaching the stomach over the vagi.<sup>5</sup> But there may also be chemical stimuli acting through the blood.<sup>6</sup>

Following partial gastrectomy, which removes the antrum of the stomach, achlorhydria is produced in a certain proportion of cases. In table 1 are shown the results reported in a previous paper.<sup>7</sup> The observations on a much larger group are now in preparation.

To study experimentally in the dog the effects of the elimination of the second or chemical phase, a transplanted subcutaneous pouch was used.<sup>3a</sup> Intra-abdominal section of the vagi, no matter how carefully performed, frequently misses some branches, especially those that may be given off just above the diaphragm. With the transplanted pouch these objections did not hold.

All connection with the vagus and splanchnic nerves and the gastric vessels was eliminated. The pouch was dependent on the abdominal wall for its blood supply. The primary, or reflex, and the intestinal phase could still act by transmitting stimuli through the blood. The response

---

3. (a) Klein, E., and Arnheim, E.: Gastric Secretion: I. A Transplanted Subcutaneous Gastric Pouch, *Arch. Surg.* **25**:433 (Sept.) 1932. (b) Ivy, A. C.: The Role of Hormones in Digestion, *Physiol. Rev.* **10**:282, 1930. (c) Babkin, B. P.: *Die äussere Sekretion der Verdauungsdrüsen*, Berlin, Julius Springer, 1928, p. 398.

4. Ivy, A. C.; Lim, R. K. S., and McCarthy, J. B.: The Intestinal Phase of Gastric Secretion, *Quart. J. Exper. Physiol.* **15**:55, 1925.

5. Babkin,<sup>3c</sup> p. 190.

6. Klein, E.: Gastric Secretion: IV. Effect of Atropine on the Secretion of Transplanted Subcutaneous Gastric Pouches, *Arch. Surg.* **26**:246 (Feb.) 1933.

7. Klein, E.: Gastric Secretion After Partial Gastrectomy, *J. A. M. A.* **89**: 1235 (Oct. 8) 1927.



to test meals of meat and water was studied (table 2). A partial gastrectomy was then performed to remove the secondary phase. After this, no free acid was secreted in the pouch during the first six hours after a meal (table 2). However, a small dose of histamine produced a

TABLE 1.—*Effect of Partial Gastrectomy on the Acidity of the Gastric Contents*

Type of Ulcer	Anacid, per Cent	0 to 20, per Cent of Patients	20 to 50, per Cent of Patients	50 and Above, per Cent of Patients	Number of Patients
<b>Duodenal</b>					
Before operation.....	..	4	36	60	50
Recent*.....	9	9	46	35	11
Old.....	25	41	17	17	12
<b>Gastric</b>					
Before operation.....	..	28	60	12	25
Recent.....	45	33	11	11	9
Old.....	100	..	..	..	3
<b>Gastrojejunal</b>					
Before operation†.....	..	11	67	22	9
Recent.....	25	25	50	..	4
Old.....	50	..	50	..	2

\* "Recent" refers to patients examined immediately after operation and "old," to patients examined six months after operation.

† "Before operation" refers to patients examined before partial gastrectomy.

TABLE 2.—*Effect of Partial Gastrectomy on the Secretion of a Transplanted Subcutaneous Gastric Pouch Deprived of Vagus and Sympathetic Nerve Supply*

Hour	Volume of Juice, Cc.	Free Hydro- chloric Acid	Total Acid
<b>Before partial gastrectomy</b>			
1.....	0.2	0	0
Fed 250 Gm. of meat			
2.....	0.6	16	33
3.....	1.1	27	54
4.....	0.7	14	43
5.....	0.8	25	50
6.....	0.6	20	45
<b>After partial gastrectomy</b>			
1.....	0.2	0	0
Fed 250 Gm. of meat			
2.....	0.5	0	0
3.....	0.2	0	0
4.....	0.2	0	0
5.....	0.6	0	0
6.....	0.4	0	0
7.....	0.2	0	0

normal response (table 3), showing that the glandular cells could respond promptly to a chemical stimulus.

When, therefore, the primary vagal phase was absent, the removal of the secondary or gastric phase by partial gastrectomy resulted in an acidity in the pouch during the period when the secretions from these two stimuli are normally present. Of course, intestinal neutralization could play no part in the anacidity occurring in the pouch.

Previous evidence showing the relation of antrectomy to the phases of gastric secretion is that of Gross<sup>8</sup> and Sawitsch and Zeliony,<sup>9</sup> who showed that chemical stimuli producing the secondary phase act not on the body and fundus but on the antrum.<sup>3</sup> Smidt<sup>10</sup> studied the secretion in dogs with Pavlov pouches, and then did a partial gastrectomy. The secretory curves were lowered in such a way as to show suppression of the secondary phase.

One may say with fair certainty, then, that partial gastrectomy removes the secondary or chemical phase of gastric secretion if it is sufficiently extensive to remove the entire antrum. Pylorectomy, which

TABLE 3.—*Effect of Histamine on the Secretion of a Transplanted Subcutaneous Gastric Pouch Before and After Partial Gastrectomy*

Hour	Volume of Juice, Cc.	Free Hydrochloric Acid	Total Acid
Before partial gastrectomy			
1.....	0.5	0	0
2.....	0.6	0	0
0.2 mg. of histamine subcutaneously			
3.....	2.6	32	56
4.....	1.2	18	45
5.....	1.0	0	25
6.....	1.0	0	10
7.....	0.5	0	0
After partial gastrectomy			
1.....	0.3	0	0
2.....	0.4	0	0
0.2 mg. of histamine subcutaneously			
3.....	2.3	12	32
4.....	1.1	12	48
5.....	1.1	0	15
6.....	0.8	0	8
7.....	0.6	0	6

is so often confused with partial gastrectomy, is not the same operation. Part of the antrum is left. Also, if the pylorus is left, some of the antrum remains.

Table 1 shows, nevertheless, a wide variation in the acid secretion following partial gastrectomy in man. The results range from anacidity (most common in cases of gastric ulcer) to hyperacidity (most common in cases of duodenal ulcer). Can any cause be assigned for these variations? Since the secondary phase has been eliminated, and since the intestinal phase starts late and apparently does not produce a high rate

8. Gross, W.: Beitrag zur Kenntnis der Sekretionsbedingungen des Magens nach Versuchen am Hund, Arch. f. Verdauungskr. **12**:507, 1906.

9. Sawitsch, W., and Zeliony, G.: Zur Physiologie des Pylorus, Arch. f. d. ges. Physiol. **150**:128, 1913.

10. Smidt, H.: Experimentelle Studien am nach Pavlov isolierten kleinen Magen über die sekretorische Arbeit der Magendrüsen nach den Resektionen Billroth I und II, sowie nach der Pylorusausschaltung nach v. Eiselsberg, Arch. f. klin. Chir. **125**:26, 1923.

of secretion, the acidity in the three hour Rehfuess tests, when it persisted after gastrectomy, would seem most likely to be due to the primary phase or to spontaneous secretion. Of course, nothing has been done to remove these.<sup>11</sup>

The amount of acid present in the test meal after the operation is, therefore, caused by the following factors:

1. The amount of secretory stimulation that persists. This is probably chiefly vagal and reflex. No doubt it is greater in some persons than in others. The possibilities of intestinal stimulation and of parenteric stimulation must also be borne in mind.

2. The relative percentage of the secretion which before operation is due to the secondary phase. For argument's sake, assume that in one case it is 30 per cent and in another 60 per cent. In the latter, partial gastrectomy would reduce the postoperative acidity much more than in the former. It is likely that the second condition is more frequent after the operation for gastric ulcer than after duodenal ulcer.

3. The amount of neutralizing substances. Pancreatic juice, bile, saliva and the test meal itself neutralize acid. That these are not, however, the sole factors in the production of anacidity, as Portis and Portis<sup>12</sup> contended, is clear from what has been stated previously.

4. A change in the secreting cells themselves. It is possible that in some cases such a change may occur. This will be discussed more fully later.

Briefly, then, the considerations thus far advanced show that anacidity results when the removal of the gastric secondary phase reduces the secretion sufficiently to permit neutralization of the remaining secretion by food and intestinal regurgitation. When a large proportion of the secretion is secondary, when the primary, or vagal, phase is not profuse and when a great amount of regurgitation is present, anacidity results; when the conditions are reversed, acidity will persist. Of course, these are the extremes, and all degrees of variations intervene.

Table 1 shows that in cases of gastric ulcer the tendency toward achlorhydria after operation is greater than in those of duodenal ulcer. Although the evidence is not conclusive, it seems highly probable that the former conditions are more often approximated in cases of gastric ulcer and the latter in those of duodenal ulcer.

A further contributing element is that in the case of duodenal ulcer the first part of the duodenum is also removed during the operation. Since inhibitory impulses to gastric secretion originate in this part

---

11. The possibility that some of the secretion of acid which persists is due to stimuli of parenteric origin also cannot be excluded.

12. Portis, S. A., and Portis, B.: *Effects of Subtotal Gastrectomy on Gastric Secretion*, J. A. M. A. 86:836 (March 20) 1926.

(Sokolov,<sup>13</sup> Smidt,<sup>10</sup> Lim, Ivy and McCarthy<sup>14</sup>), the removal of these inhibitions tends to permit greater secretion after operation in cases of duodenal than in those of gastric ulcer.<sup>15</sup>

For these reasons, as stated in a previous paper,<sup>16</sup> section of the left, or anterior, vagus has been added to the operation of partial gastrectomy when the preoperative acidity is very high. The additional reduction of part of the primary vagal phase is usually sufficient to produce achlorhydria.

There is, however, one further element that enters into the production of anacidity after operation for both duodenal and gastric ulcer. This is shown by studies with histamine. When using histamine as a gastric stimulant, one should recognize clearly that the resultant stimulation is not exactly comparable to that of the test meal. First, histamine is a powerful chemical stimulus acting directly on the cells and stimulating chiefly the secretion of hydrochloric acid;<sup>17</sup> second, the primary or vagal phase does not enter into the resultant secretion, and, third, the juice secreted into the stomach is obtained in a purer state, since no food from a test meal is mixed with it. These facts should be remembered when comparisons are made with the various secretory tests in man.

After partial gastrectomy histamine tests were performed on seventeen persons who showed an anacidity to the Rehfuess test meal with gruel. All of the patients had free acid before operation. Five-tenths milligram of histamine hydrochloride was injected subcutaneously, and the gastric secretion was extracted every fifteen minutes for three hours. All but four of the patients showed acid after injection of the histamine. The degree varied from a small amount in only one tube to the presence of free acidity throughout the three hours of the test.

In these cases it is evident that acid could still be secreted. However, the amount had been so reduced by the operation that with the ordinary stimulus of the test meal the resultant acid secretion could be neutralized by food and intestinal regurgitation. It should be emphasized that the results which follow stimulation by food are probably more in line with

---

13. Sokolov, quoted by Pavlov.<sup>2b</sup>

14. Lim, R. K. S.; Ivy, A. C., and McCarthy, J. B.: Contributions to Physiology of Gastric Secretion by Local and Chemical Stimulation, *Quart. J. Exper. Physiol.* **15**:13, 1925.

15. Experiments are now under way to determine whether some part of the preoperative hyperacidity so common in cases of duodenal ulcer is due to interference with inhibition from the duodenum.

16. Klein, E.: Left Vagus Section and Partial Gastrectomy for Duodenal Ulcer with Hyperacidity, *Ann. Surg.* **90**:165 (July) 1929.

17. Babkin, B. P.: The Value of Histamine as a Test of Gastric Secretion from a Physiological Point of View, *Canad. M. A. J.* **23**:268, 1930.

the conditions under which the patient lives than those which are present after a powerful chemical stimulant on the gastric cells in an empty stomach.

In four patients the secretion did not respond to food or histamine. In one, free acid was present in only one sample, and in two others, in two samples extracted at the fifteen minute intervals. Histamine is one of the most powerful stimulants of secretion of hydrochloric acid known, and since, as already stated, it acts directly on the gastric cells, the most likely explanation of the anacidity is that some change occurred in the secretory cells.

What the change is or why it occurs I do not know. Sections of the fundus have been examined for many years after partial gastrectomy, and they appear normal.<sup>18</sup> But gastric mucosa that looks normal under the microscope may occur with achylia, and besides no specimen has been examined microscopically in which anacidity to histamine has been found after operation. Possibly a spread of the gastritis present in nearly all cases of ulcer is responsible, but as yet I do not know. Bearing on this problem is the work of Winkelstein,<sup>19</sup> who reported that after partial gastrectomy 55 per cent of stomachs do not excrete neutral red. Since excretion of the latter is supposed to be suppressed only in the presence of true anacidity, the presumption was that true achylia existed in those cases.

Comfort and Osterberg<sup>20</sup> found that 20 per cent of their subjects showed anacidity with histamine after partial gastrectomy. No report was made of the percentage of anacidity following the ingestion of food. They conclude, in view of the small proportion of anacidity with histamine, that the gastric, or secondary, phase of secretion is not of great importance. But it should be evident that this conclusion, though it may be true, is not a necessary consequence of their work. Histamine is similar to the chemical stimulant of the second phase. To use it after partial gastrectomy is to supply a stimulus similar to the one removed. The surprising thing is that any subject shows anacidity after the use of histamine, for the acid cells are still present. As already stated, it seems necessary to assume some changes in the secreting cells to account for this. Whatever the cause, there can be little doubt that it is associated with the partial gastrectomy. This unknown factor may also be partly

---

18. Thus a patient operated on for gastric polyps five years after gastrectomy for ulcer showed normal mucous membrane in the stomach (microscopic examination). There was no recurrence of the ulcer.

19. Winkelstein, A.: Gastric Secretion After Partial Gastrectomy for Ulcer, *Am. J. Surg.* 7:494, 1929.

20. Comfort, Mandred W., and Osterberg, Arnold E.: Gastric Secretion After Stimulation with Histamine, *J. A. M. A.* 97:1141 (Oct. 17) 1931.

responsible for the progressive reduction in acidity previously reported in many cases of partial gastrectomy in which acidity was present after the operation.<sup>7</sup>

In conclusion I would emphasize that although it is of the utmost importance to accumulate as many facts concerning gastric secretion as possible, any comparisons of the results should be accompanied by a realization that the mechanisms involved may not be identical. It is, to mention one instance, justifiable to compare the secretion after the injection of histamine to that obtained after the ingestion of food; but the factors involved are not the same. And they are not the same because gastric secretion due to food is not the pouring out of hydrochloric acid and pepsin as a response to one type of stimulus, but a series of responses to stimuli arising from many sources, acting through different channels and effected in various ways. The era of the Ewald tests, with the examination of a single specimen after a test meal, was followed by that of the Rehfuess tests, with fractional examinations for two or three hours. Attention should now be focused on the separate phases of secretion, to study them individually in both normal and pathologic conditions.

#### SUMMARY AND CONCLUSIONS

Gastric secretion is the total of various distinct phases of secretion in response to stimuli acting at different points.

The three chief phases are: (1) the primary, due to reflexes from various sensory organs reaching the stomach over the vagus nerve; (2) the secondary, or gastric, due to chemical stimulation of the antrum, and (3) the intestinal. In addition to these there is the spontaneous secretion, part of which seems to be due to conditioned reflexes.

Some stimuli, such as food, excite all the phases, whereas other stimuli, such as histamine, stimulate the secreting cells directly and seem to be similar to the stimuli effecting the second phase.

The removal of one phase, as by sectioning the vagi or by removal of the antrum, leaves the other phases.

If the secretion of the remaining phases is collected in a gastric pouch (Pavlov), it is not neutralized by intestinal regurgitation, and free acid can be demonstrated. As far as I know, the concentration of hydrochloric acid secreted by the various phases is the same. If, therefore, one phase is removed and if secretion of acid persists in the pouch, there is no reason to expect the concentration of that secretion to be lowered. If the secretion is collected from the stomach the free acid may be partly or completely neutralized, producing pseudo-anacidity.

Partial gastrectomy removes the second or gastric phase. Whether anacidity results in the stomach after the ingestion of food depends on: (1) the amount of secretion which has been caused by the second phase;

(2) the amount of secretion of the other phases which are left, and (3) the amount of neutralization due to the food, intestinal regurgitation and saliva. When 3 is sufficient to neutralize 2, anacidity results. The patients show free acid after the injection of histamine.

In addition to pseudo-anacidity after partial gastrectomy for ulcer in man, a true anacidity develops in some patients. In these there is anacidity both to food and to histamine. This may be due to changes in the secreting cells themselves.

Partial gastrectomy (removal of the second phase) in a dog with a transplanted subcutaneous gastric pouch which has no nervous stimulation and hence no primary phase produces anacidity in the pouch for six hours. Prior to the gastrectomy the pouch secretes acid from the first hour. The pouch continues to respond normally to histamine.

# FIFTY-FIFTH REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

JOHN G. KUHNS, M.D.

EDWIN F. CAVE, M.D.

SUMNER M. ROBERTS, M.D.

AND

JOSEPH S. BARR, M.D.

BOSTON

JOSEPH A. FREIBERG, M.D.

CINCINNATI

JOSEPH E. MILGRAM, M.D.

NEW YORK

AND

ROBERT I. STIRLING, F.R.C.S. (EDIN.)

EDINBURGH, SCOTLAND

*Concluded from page 1082*

## NEOPLASMS

*Tumors of Bone.*—Brailsford<sup>25</sup> pointed out that while the "barrier action" of the epiphyseal cartilage to bacteria and tumor cells is great, the breaking down of the barrier by a destructive lesion, as demonstrated by a roentgenogram, does not necessarily indicate that the lesion is malignant, as lesions of a tuberculous nature frequently act in this manner.

*Radiosensitivity of Tumors.*—Stewart<sup>26</sup> reviewed extensively the relative radiosensitivity of benign and malignant tumors. This article, replete with the experiences of the author, merits reading. The tumors were discussed according to their tissue origin.

*Review of Ewing's Tumor.*—Lattman<sup>27</sup> stated that Ewing's tumor should be diagnosed on the basis of the history of the clinical and roentgenologic findings and, above all, of the radiation therapeutic test. Biopsy was deprecated on the grounds that early metastases may follow. The tumor, which is most common in males under 30 years of age, is usually situated in the middle of the bone and never in the epiphyses. While there is occasionally a formation of new bone, normally the tumor causes definite destruction of the cortical and central portions of the

25. Brailsford, J. F.: Brit. J. Radiol. 7:233, 1934.

26. Stewart, F. W.: Radiosensitivity of Tumors, Arch. Surg. 27:979 (Dec.) 1933.

27. Lattman, I.: Brit. J. Radiol. 7:194, 1934.



bone. Irradiation is the most satisfactory form of treatment, and amputation should be reserved for cases in which the condition of the soft tissues precludes further irradiation or in which pain is unbearable.

*Benign Giant Cell Tumor of Bone.*—Holland<sup>28</sup> expressed the opinion that the roentgenologic appearance of a benign giant cell tumor of bone, i. e., a self-contained uniform expansion, an area of internal destruction and the shadows of the bony trabeculae, is insufficient to warrant a definite diagnosis, but that a long history is of assistance in making a diagnosis. He cited five cases of the tumor in unusual locations: in the shaft of the fibula, in the shaft of the humerus, in a rib, in the ischial tuberosity and in the patella.

*Roentgenologic Characteristics of Echinococcus Disease in Bone.*—Claessen<sup>29</sup> reported four more cases of echinococcus disease of bone and reviewed those that had previously been reported in the medical literature. He expressed the opinion that sporadic cases may be found anywhere and that a knowledge of the roentgenologic appearance is important, since from 1 to 2 per cent of cases of echinococcus disease appear in bone. One third of these cystic tumors are found in the pelvis; the spinal column is next in frequency of involvement. In the author's cases, the disease was found in the iliac bone, in the sacrum, in the head of the femur and in the diaphysis of the femur and of the fibula. In bone, the cyst is not surrounded by a strong fibrous capsule. There is practically no regional atrophy of bone and no periosteal reaction. The appearance is that of an expansive growth extending from the centrum outward. The limits of the disease can rarely be determined by roentgen examination.

#### MISCELLANEOUS

*Synovial Sheaths and Fascial Spaces of the Hand.*—Three excellent drawings of dissections demonstrating the topographic anatomy of the hand were shown by Hughes-Jones.<sup>30</sup> Their value is enhanced by the fact that the palmar creases are superimposed, which gives an easy means of locating the position of the synovial sheaths and the fascial spaces.

*Improved Technic for Examination of the Shoulder.*—A method of obtaining a satisfactory roentgenogram of the shoulder was described by Fergusson.<sup>31</sup> First, the patient is placed in a supine position on a Potter-Bucky diaphragm, with the uninjured shoulder raised by pads. The film is suitably centered. The rays actually passing through the glenoid fossa are oblique. Next, the patient is helped over into an

28. Holland, C. T.: Brit. J. Radiol. 7:277, 1934.

29. Claessen, G.: Acta radiol. 15:178, 1934.

30. Hughes-Jones, W. E. A.: M. J. Australia 2:658, 1933.

31. Fergusson, J. N.: Brit. J. Radiol. 7:33, 1934.

almost prone position, the uninjured shoulder again being raised by pads. The film, placed as before, caused the oblique rays to pass through the scapula so that the bone appears scarcely broader than its axillary border. A kilovoltage of about 65 is used for the first film, and of 80 for the second. A less satisfactory result can be obtained by the use of an erect Potter-Bucky diaphragm, with the patient in the upright position.

*Osteochondritis Dissecans: Intra-Articular, Osteocartilaginous Loose Bodies.*—Conway<sup>32</sup> based his discussion on observations on ten cases of osteochondritis dissecans. The well known theories of etiology—trauma (acute or due to faulty bearing of weight), infection and mycotic embolism—were discussed. The pathologic aspects and the symptoms were dealt with. The knee was involved in eight cases and the elbow in two, which is, roughly, the usual ratio. The loose bodies usually arise in the knee, from the lateral portion of the internal condyle. They may arise from the patella or may be synovial chondromas. The best time for the removal of the loose body is during the period of demarcation before synovial change has occurred.

*Posttraumatic Acute Bone Atrophy (Sudeck's Atrophy).*—Gurd<sup>33</sup> discussed acute atrophy of bone, which may be trivial, but which usually occurs with injury near a joint. The atrophy involves the small bones of the hands and feet more frequently than the shafts of long bones. The author offered the explanation that the cause of the condition is a stimulus of the reflex arc, with secondary local hyperemia and absorption of bone. The cure may be slow, but diathermy is of value, and in the treatment of weight-bearing joints, protected weight bearing in plaster is most important in speeding recovery.

#### ORTHOPEDIC OPERATIONS

*Treatment of Pyogenic Osteomyelitis of the Sacro-Iliac Joint by the Bardenheuer-Picque Resection, Modified by the Orr Method.*—Kulowski,<sup>34</sup> from a review of thirty cases of pyogenic sacro-iliac infection seen in Steindler's clinic, concluded that results by any method other than resection of the joint are poor because of inadequate drainage. He reported in detail four cases in which the patient was treated by complete or partial resection of the joint by the Bardenheuer-Picque technic. The posterior half of the ilium was exposed subperiosteally, both intrapelvic-ally and extrapelvic-ally, carrying the exposure down to the sciatic notch. The ilium was then sectioned vertically through both tables, and the flap levered out by driving a chisel into the sacro-iliac joint. The resection in some instances was partial, a bridge of bone being left just above

32. Conway, F. M.: Ann. Surg. 99:140, 1934.

33. Gurd, F. B.: Ann. Surg. 99:449, 1934.

34. Kulowski, J.: Am. J. Surg. 23:305, 1934.

the sciatic notch; in others the posterior part of the ilium was removed. The sacral cartilage and necrotic bone were then removed with a chisel and a curet until normal bone was reached. Any intrapelvic abscess was evacuated by blunt dissection in the depths of the wound. The wound was then loosely packed with petrolatum gauze, and the pelvis was immobilized in a double plaster spica. In the last four cases in which this treatment was used there were no deaths, but sufficient time has not elapsed for a final study of the end-results.

*End-Results of Arthroplasties of the Hip.*—Campbell, in 1927, reported a study of the end-results of arthroplasties of the hip. With the increased experience and further study which the lapse of time has afforded, he reported<sup>35</sup> a total of one hundred and twenty-seven arthroplasties done on ninety-four patients. The operation consisted of the remodeling of the acetabulum and the head of the femur and the interposition of a double layer of fascia lata. He used the Smith-Petersen approach, being most careful not to strip off the soft tissues from the neck of the femur, so preserving its blood supply and preventing aseptic necrosis. He permitted walking after from four to six weeks if roentgenograms showed satisfactory bone structure. He concluded that arthroplasty should be undertaken in cases of nonarticular disease of the hip which has become quiescent. Exceptions are made in persons with tuberculosis or unsettled compensation and in the cases of men doing heavy labor. He considered treatment in bilateral cases to be much more difficult, the end-results on the whole being unsatisfactory, but he expressed the belief that more careful study might yield better results. Of forty-four nonarticular cases with known end-results, in 60 per cent the results were excellent and in 22 per cent, good; in 18 per cent the results were poor or there was failure.

*Results of Operative Treatment of Wry Neck.*—Arnold<sup>36</sup> analyzed the end-results following operative procedures for wry neck in the clinic at Danzig. Four methods of correction were reviewed: subcutaneous tenotomy, open tenotomy, open division of the muscle and total or partial extirpation of the muscle. The best functional and cosmetic results were obtained following open tenotomy of the sternocleidomastoid muscle at the mastoid process, with full correction of the deformity and painstaking after-care. For patients over 15 years of age, or for those, particularly males with very severe cases, total or partial extirpation of the muscle was recommended.

#### FRACTURES

*Treatment of Fractures of the Upper End of the Humerus.*—After studying the mechanics of the shoulder joint on a skeleton to which

35. Campbell, W. C.: J. Michigan M. Soc. **33**:49, 1934.

36. Arnold, W.: Arch. f. klin. Chir. **178**:257, 1934.

artificial elastic muscles has been attached, Howard and Eloesser<sup>37</sup> reached several interesting conclusions. The much used abduction treatment of fractures of the surgical neck of the humerus is wrong, theoretically and clinically. The displacement of the distal fragment is produced by the abductor muscles of the shoulder, the latissimus dorsi, the teres major and the pectoralis major. Abduction of the arm increases the pull of these muscles. The authors concluded that if the long head of the biceps is intact, fractures of the surgical neck of the humerus may be reduced most readily by traction on the arm in a neutral position (not abducted), with a simultaneous manual manipulation of the distal fragment. If the long head of the biceps is ruptured open, operation should be resorted to if satisfactory reduction is to be accomplished. After reduction, the most stable position of the fracture is with the arm bandaged to the body over a small axillary pad.

*Reduction of Fractures of the Surgical Neck of the Humerus.*—In cases of fracture of the surgical neck of the humerus which have resisted the normal methods of setting, Anderson<sup>38</sup> advocated that the proximal fragment be controlled by a bone-awl, which is introduced through a stab wound on the outer aspect of the shoulder and partially transfixes the bone. Subsequent steps are carried out under the fluorescent screen. Traction is exerted in the line of the arm, and while the traction is maintained the arm is adducted across the chest. The abducted upper fragment is then brought into apposition by depressing the bone-awl. Last, the arm is brought slowly to a slightly abducted position.

*Treatment of Fractures of the Radius and Ulna: New Anatomic Method of Treatment.*—Anderson<sup>39</sup> has devised a special form of portable apparatus for skeletal traction and countertraction for the reduction of fractures of the forearm. The apparatus consists of a duralumin frame with a horseshoe base at either end. One pin was passed through the upper end of the ulna, and a half-pin is passed into, but not through, the lower end of the radius. An aluminum cuff fits over the ulnar side of the forearm to prevent rotation. Rotation of either the upper or the lower fragment can be produced by turning either horseshoe base. The apparatus can be modified to care for fractures of the lower end of the humerus or of the olecranon. After the reduction is complete the arm is incorporated in a cast at a right angle.

*Fracture of the Tibial Spine.*—Venable<sup>40</sup> stated that the usual cause of fracture of the tibial spine is a pull of a strong cruciate ligament

37. Howard, N. J., and Eloesser, L.: J. Bone & Joint Surg. 16:1, 1934.

38. Anderson, H. M.: Brit. M. J. 1:232, 1934.

39. Anderson, R.: J. Bone & Joint Surg. 16:379, 1934.

40. Venable, C. S.: Am. J. Surg. 24:478, 1934.

when the leg is fixed and the body is rotated or when the body is fixed and the lower part of the leg rotated. The clinical signs are extreme pain, rapid bloody effusion of the knee joint and limitation of motion. Prompt removal, he stated, is the only way to prevent deformity, and there is little, if any, disturbance of stability in the knee after such a procedure.

[*Ed. Note.*—Removal of the fractured tibial spine is not always necessary. Open reduction has given a good result in the experience of the editors.]

*Treatment of Compound Fractures of the Tibia.*—Simpson-Smith<sup>41</sup> gave an account of a method of treating compound oblique or transverse fractures of the tibia which he had carried out in twenty cases. After preparation of the leg, an incision 5 inches (12.7 cm.) long was made, a thorough débridement was carried out and the wound was washed with acriflavine hydrochloride. The periosteum was not opened, but the subcutaneous surface and anterior and postero-internal borders of the tibia were cleared for 1 inch (2.5 cm.) above and below the fracture. The fragments were brought into line by the traction of an assistant on the foot and the use of Lane's forceps. A special clamp which gripped the exposed borders was applied, and before it was tightened the fragments were thrust home. A sterile gauze roll was next applied, covering the wound and surrounding the clamp. A skin-tight sterilized plaster case was applied from the middle of the thigh to the toes, the foot being slightly flexed in a plantar position. When the plaster was dry, a window was cut to expose the wound, and the clamp was removed. The wound was sutured, with the exception of a small portion at the bottom. After six weeks or longer the plaster was removed, a short plaster cast with a Böhler's walking iron was applied and the patient was encouraged to walk with it for a few more weeks, by which time the union was firm.

*Absorbable Metallic Material in Bone Surgery.*—Verbrugge<sup>42</sup> treated twenty-one fractures in various parts of the body with magnesium bolts, screws or staples, as the case demanded. The material was completely absorbed, but the process was slow enough to permit the formation of callus. Small amounts of magnesium were absorbed in three or four months, and larger amounts lasted correspondingly longer. No trace of metal was found after two years, but in many cases the exact time of its disappearance was unknown. Absorption was accompanied by the production of hydrogen, which caused no symptoms. No toxic or irritating symptoms were observed. The maximum amount of magnesium introduced was 5 Gm.

41. Simpson-Smith, A.: *Brit. M. J.* **2**:1019, 1933.

42. Verbrugge, J.: *Presse méd.* **42**:460, 1934.

RESEARCH

*Investigation on the Osseous System of the New-Born.*—Tøverud<sup>43</sup> analyzed the skull bones and ribs of one hundred infants who died at or shortly after birth. He found a subnormal amount of ash and a low calcium content in the bones of infants whose mothers had received an insufficient amount of food during pregnancy. The calcium content was depleted more than the phosphorus content. More marked depletion was shown in premature infants or in twins born of malnourished mothers. There was an increase in the osteoid tissue, with small osteocytes and a lack of intercellular substance in the children of malnourished mothers. Tøverud expressed the opinion that these changes are closely related to the osteoporosis and rickets seen during early postnatal life.

*Effect of Low Calcium Content on Osteogenesis and Healing of Fractures.*—Key<sup>44</sup> resected bone from the ulnas of twenty dogs. One side was used as a control. In the defect on the other side, various substances containing calcium were introduced, and the process of healing was followed both by roentgen examination and by subsequent inspection of the lesions. Key concluded that neither calcium phosphate and carbonate in the proportions in which they occur in bone nor bone powder, made by removing the organic matter from bone, appeared to stimulate osteogenesis of bone when implanted in a bone defect.

*Small Bone Grafts.*—Keith<sup>45</sup> transplanted small bone grafts into defects in the radius in young and adult dogs. In one series, chips of bone were placed about and between the end of the bone, a section of bone and periosteum having been removed. In four experiments there was almost complete bridging of the gap in from twenty to thirty-five days. Union was often more definite at the proximal end than at the distal end. Mild weight bearing was considered favorable to union. It was considered unwise to fragment a bone graft more than necessary, since to do so destroys somewhat its supporting and osteogenic functions. The formation of new bone from the grafts was much more marked in young than in adult dogs, and this tendency was dependent on the presence of living osteogenic cells in the grafts. It was emphasized that an intact blood supply of the bed of the graft and the combined layer of the periosteum is important. From the experiments there is no evidence that metaplasia of other connective tissue cells to bone-forming cells plays a part in the formation of new bone associated with bone grafting.

43. Tøverud, K. V.: *Ztschr. f. Kinderh.* 56:56, 1934.

44. Key, J. A.: *J. Bone & Joint Surg.* 16:176, 1934.

45. Keith, W. S.: *J. Bone & Joint Surg.* 16:314, 1934.

*Experimental Transplantation of Bone with Special Reference to the Effect of Decalcification.*—Ghormley and Stuck<sup>46</sup> reviewed extensively the literature on the transplantation of bone and carried out experiments on adult dogs which seemed to show that the best fusion of the bone transplant to surrounding bone resulted when a cancellous graft removed either from the iliac crest or from the tibia was used. Cortical grafts did not die but showed diminished condensation, and pure periosteal transplants did not form new bone. The authors speculated that in young animals, or in children, periosteum may produce new bone when transplanted. Bone chips alone, as used in the Hibbs method of spinal fusion, gave good fusion, but not as good as that produced by the cancellous graft. Animals placed on a decalcifying diet prior to the transplantation of bone gave evidence of more active production of new bone both around the cortical and around the cancellous transplants.

*Experimental Studies of Reparative Costal Chondrogenesis and Transplanted Bone.*—Bisgard<sup>47</sup> demonstrated in patients in whom the costal cartilages had been resected, and also in dogs, that the perichondrium has little if any power to regenerate cartilage. He therefore advocated the immediate transplantation of osteoperiosteal grafts to the chondrectomized perichondral beds to bridge the gap from the rib to the sternum.

*Experimental Tuberculosis of the Bones and Joints in Rabbits.*—Trudel<sup>48</sup> was able to produce tuberculous infection in rabbits by the injection of a suspension of tubercle bacilli into the nutrient artery of the femur. A typical tuberculous condition developed in the knee joints in the majority of the animals, provided the animals had been sensitized to tuberculosis previously. Otherwise, the animals either recovered or died of generalized tuberculosis. In 75 per cent of the sensitized animals, Trudel found that after the bone lesion developed there was no other detectable focus.

[ED. NOTE.—This work is of greatest importance, because it shows again that tuberculous lesions of the bone are rarely, if ever, the primary lesion, although the primary lesion may be healed.]

46. Ghormley, R. K., and Stuck, W. G.: *Experimental Bone Transplantation, with Special Reference to Effect of "Decalcification,"* Arch. Surg. 28:742 (April) 1934.

47. Bisgard, J. D.: Surg., Gynec. & Obst. 58:817, 1934.

48. Trudel, P. J.: Am. Rev. Tuberc. 28:331, 1933.

# ARCHIVES OF SURGERY

VOLUME 30

FEBRUARY 1935

NUMBER 2

## ETIOLOGY AND TREATMENT OF CLAWFOOT

REPORT OF THE RESULTS IN ONE HUNDRED AND TWO FEET  
TREATED BY ANTERIOR TARSAL RESECTION

JOHN T. SAUNDERS, M.D.\*

NEW YORK

The many theories regarding the cause of clawfoot and the wide variety of methods of treatment indicate that the true nature of the deformity is not yet known. Interest in the condition lies in the lure of the unknown, the more so because most of the acquired human deformities have been adequately explained.

Observations on the occurrence, progress and response to treatment of over 400 cases of clawfoot at the New York Orthopaedic Hospital during the past three and one-half years are the basis for this study. The report includes a discussion of the etiology with evidence pointing to the spinal cord as the location of the causative lesion, a review of treatment, and the end-results in 102 feet treated by anterior tarsal resection.

The terms *pes cavus*, *talipes arcuatus*, *talipes plantaris*, hollow or contracted foot, *griffe pied creux*, *Hohlfuss* and nondeforming clubfoot have been used to designate the deformity.

The typical condition presents an exaggeration in the height of the longitudinal arch with slight shortening of the foot, prominent metatarsal heads, clawing of the toes, loss of flexibility in all the joints of the foot, reduction of treading surface and often a limited dorsal flexion at the ankle joint.

### DESCRIPTION

Clawfoot is considered a distinct deformity and differs from paralytic calcaneus or equinus associated with an exaggerated longitudinal arch and from other distortions of the foot resulting from known muscular weakness in that these deformities lack early stiffness of the foot and clawing of the toes. Clawfoot develops most often during adolescence and is about as common in boys as in girls. No relationship with race or social status has been demonstrated.

A mild degree of this condition occurs frequently and is often considered a well formed foot with a high arch rather than a deformity.

\* Fellow of New York Orthopaedic Dispensary and Hospital.

Submitted in January 1934 in partial fulfilment of the requirements for the degree of Doctor of Medical Sciences in the Faculty of Medicine of Columbia University.



The deformity disappears on standing, and it is possible to correct it by applying pressure under the head of the first metatarsal. At a somewhat later stage the high arch becomes obvious and the ball of the foot very prominent; the toes become hyperextended at the metatarso-phalangeal joints and flexed at the interphalangeal joints. Dorsal flexion of the foot is usually limited. This limitation may be due to a contracted calf or to a deformity within the foot; usually it is a combination of both factors. In clawfoot of marked degree the cavus becomes very conspicuous and does not disappear on standing. Occasionally flexibility is progressively lost until the foot is almost rigid. The toes become markedly clawed, stiff and, in extreme cases, dislocated dorsally. The width of the foot is increased at the level of the metatarsal heads, and callosities develop under them owing to increased pressure at these points as a result of stiffness and diminished treading surface. The equinus type of deformity is often such as to make it impossible for the patient to stand with the heel touching the floor. There is frequently an associated moderate varus position of the heel and slight adduction deformity of the forefoot.

#### SYMPTOMS

The symptoms of mild cases are often voiced by the parents, who complain that it is difficult to find comfortable shoes for the child or that shoes become misshapen and wear out quickly. It is not uncommon to find on the dorsum of the foot tender areas resulting from pressure of the shoes. Easy fatigue and weak ankles are frequent complaints. As stiffness and deformity develop the gait becomes ungraceful and jarring, awkwardness is noted, and stumbling occurs.

Callosities appear with the more marked deformity and cause great discomfort. They usually develop under the first and fifth metatarsal heads, and in extreme cases ulcers arise in them. Corns develop early from pressure of the shoes on the knuckles of hammer toes. The friction and pressure against the shoe at these points are increased at each step by the action of the long extensors of the toes in their attempt to assist in dorsal flexion of the foot. Clawfoot may be a most distressing and disabling condition, leading patients to agree to any procedure which promises relief.

#### HISTORY

Clawfoot with marked equinus deformity is probably the condition described by Andry in 1741 as "bolt feet":

They hide this deformity by wearing shoes of the ordinary shape, but having that part within which the foot leaves a void, filled up with a bit of cork, or stuffed with flocks . . . it is not absolutely incurable; but it may be helped if not cured by pulling frequently, but very gently, the toes of the child.

The treatment advocated by Andry, in addition to prescriptions for soaking the foot in tripe broth and for rubbing the calves with oil of worms, consisted of replacing wooden heels by lead and advising stretching of the calves by mountain climbing.

In the middle of the nineteenth century clawfoot was confused with, and described as, a variety of congenital and acquired clubfoot. Little (1853) described it as a separate condition. He suggested rheumatic inflammation as its cause and used tenotomies in treatment. Barwell (1865) included a description of clawfoot in his book "On the Cure of Clubfoot Without Cutting Tendons." He thought that the cause was a weak muscle in the calf and treated the deformity by using rubber springs to assist this group of muscles. Duchenne (1863) described the action of the intrinsic muscles of the foot and gave as his theory of the production of clawfoot a weakness of the muscles supplied by the lateral plantar nerve. This theory has had a profound influence since its publication and is accepted as the most satisfactory explanation by many authors today. Golding-Bird (1883), in England, could not confirm Duchenne's observations and suggested weak peroneal muscles as the cause of clawfoot. Fisher (1889) also disagreed and contributed to the literature by suggesting transient weakness of the dorsal flexors of the foot, due to childhood fevers, as the etiologic factor. Shaffer (1885) published some interesting observations on infantile paralysis and contributed the term "nondeforming clubfoot." He stated that he had noted quite frequently, as early as 1865, that when both lower extremities had been paralyzed and had apparently entirely recovered, or in some cases in which there was unilateral paralysis, abnormalities appeared in the supposedly sound limb.

The work of recent writers shows a continued endeavor to find an adequate explanation for this deformity as well as some procedure to secure lasting relief. Hoffman (1912) devised an operation for severe grades of clawed toes which consisted of resection of all the metatarsal heads. Forbes (1913) described the difficulties of treatment and advised transplantation of the long toe extensor tendons to the necks of the metatarsals. Steindler (1917) published a description of his well known stripping operation for the release of the plantar fascia. In 1921 he wrote that this procedure alone was not sufficient in many cases and advised resection of bone to correct the cavus deformity. In 1919 Hibbs published his method of transplanting the long toe extensor tendons to the cuneiform bones. Recent European literature has described radical surgical procedures as necessary to assure permanent correction of the deformity. Numerous articles have appeared describing associated spina bifida occulta and thickening of the dura mater of the spinal cord. A comprehensive monograph on clawfoot, with an almost complete bibliography, was published by Hackenbroch (1926).

He recognized the progressive nature of the condition and recommended complete correction of the deformity by resection of bone and by transplantation and lengthening of tendons.

#### ETIOLOGY

Clawfoot may be associated with many known conditions or may occur without demonstrable cause. The literature contains numerous references to its cause or causes, whereas some authors state that there is no evident etiologic factor. Because he could find no adequate explanation for clawfoot Mills (1924) was drawn to a study of it. He wrote:

. . . on consulting a standard textbook on orthopaedic surgery I found eight separate causes given for this singularly precise and definite deformity. The impression left on my mind from reading the list was one of surprise that anyone managed to escape the disease. I was also reminded forcibly of the remark of one of my surgical teachers to the effect that, when a number of different forms of treatment were given for one disease, no one of them was satisfactory.

The theories of etiology which are most frequently advanced are discussed later. They are: congenital origin, acute illnesses of childhood, constriction of the feet during growth, intrinsic and extrinsic muscular imbalance, paralysis in the foot following poliomyelitis, diseases of the central nervous system, heredity, trauma and infection.

#### CONGENITAL ORIGIN

Cases known to be of congenital origin are rare, and few physicians claim to have seen one. The condition is supposed to be due to defective development of the spinal cord or to an imperfect formation of the plantar structures of the foot. Goff (1933) reported a case in a fetus of 7½ months with congenital syphilis. European writers suggest that spina bifida occulta is the cause of the "idiopathic" group of cases. They observe that at birth the spinal cord ends at the level of the third lumbar vertebra, and when adult life is reached, at the first lumbar vertebra. Accordingly they claim that with the growth of the bony canal away from the lower end of the spinal cord and the presence of congenital adhesions, traction is exerted on the nerve structures. A case with spontaneous correction of the deformity in the foot following laminectomy in a patient with spina bifida occulta was reported by Kochs (1927). Spina bifida or other congenital abnormalities which involve the spinal cord have been described as the cause of clubfoot as well as of clawfoot. In his book, "Congenital Club-Foot," Brockman (1933) stated that clubfoot and spina bifida, when occurring together, are not interdependent but coincident. He referred to the work of Parker and Shattock (1884), who showed that in these cases nerves and muscles, when examined macroscopically and microscopically, exhibited nothing abnormal. He also referred to Harrison (1904),

who demonstrated that muscle fibers developed independently of the influence of the nervous system. Duncher (1913) stated that occult spina bifida was present in 80 per cent of his cases of clawfoot. At this hospital spina bifida occulta has been found to occur incidentally in 20 per cent of patients with scoliosis, none of whom had obvious clawfoot deformity.

#### ACUTE ILLNESSES OF CHILDHOOD

According to some authors acute illnesses of childhood such as measles, scarlet fever and chorea are etiologic factors. Fisher (1889) stated that during such an illness there is a transient paralysis of the dorsal flexors of the foot and that subsequently the child is weak and awkward for a few weeks. Then apparent recovery takes place and later, as the foot grows, the plantar fascia does not keep pace, and arching results. Shaffer reported having seen slight hemiplegia following scarlet fever and diphtheria and suggested that when this occurs the bones grow faster than the muscles and thus cause deformity. This theory does not appear sound since in many cases with paralysis or weakness of the dorsal flexors of the foot from a known cause, such as poliomyelitis, a clawfoot does not develop.

#### CONSTRICTION OF THE FEET DURING GROWTH

The wearing of shoes which do not fit or of tight shoes with high heels and the consequent habitual disuse of dorsal flexion are described as a cause of clawfoot. Boys usually wear well shaped shoes but exhibit the deformity as often as girls, and in girls clawfoot develops before improper shoes are worn. The occurrence of unilateral cases contradicts this theory.

A high longitudinal arch and limited dorsal flexion is occasionally seen in professional dancers, who use the muscles of the calf excessively. Some writers draw an analogy between clawfoot and the bound feet of Chinese women, but in the latter there is a calcaneocavus deformity without clawing of the toes.

#### MUSCULAR IMBALANCE

*Intrinsic Muscular Imbalance.*—Paralysis of the intrinsic muscles of the foot with active extrinsic muscles is the mechanism most frequently accepted as the cause. According to Duchenne the deformity occurs as follows: The normal action of the interossei is to flex the first phalanges of the toes and extend the last two. These therefore offer a resistance to the action of the long and short extensors, which alone overextend the first phalanges and flex the last two. If the action of the long and short extensors is unopposed by the interossei the toes are drawn back onto the metatarsal bones, the heads of which are depressed

and the bases raised, so that the arch is increased and a contraction of the plantar fascia follows.

There is substantial evidence against this theory. No definite paralysis or weakness of these muscles has been demonstrated by examination, by electrical stimulation or by dissection of a typical clawfoot. In many persons with clawfoot who have been personally examined there was sufficient control of the toes to allow the presence of active interossei and lumbricales to be demonstrated. In the presence of active interossei and lumbricales hammer toe is readily produced by the exaggerated action of the long toe extensors in their attempt to aid in dorsal flexion of a foot which has already lost its flexibility owing to a cavus or equinus deformity. It can be demonstrated on a cadaver that tension on the long toe extensor and flexor tendons at the same time produces hammer toe. The intrinsic muscles of the foot are well developed structures and constitute a moderate portion of the muscle mass of the foot; therefore marked atrophy should be detectable by inspection and palpation. In poliomyelitis the intrinsic muscles are less often paralyzed than the extrinsic.

*Extrinsic Muscular Imbalance.*—The disturbance of muscular balance necessary to produce clawfoot has been ascribed to each group of extrinsic muscles. Some observers suggest that the balance of power in the foot is triangular, the three forces being the dorsal flexors, the intrinsic muscles of the sole and the muscles of the calf. They state that any disturbance of balance between them allows a cavus deformity to develop. Hammer toes are thought to be secondary.

Weakness of the peroneus longus, allowing the tibial muscles to overact, is the explanation offered by Golding-Bird. He stated that this imbalance would take the tension off the plantar fascia, allow it to contract quickly and render the cavus permanent. On the other hand, according to Tubby (1896), exaggerated action of the peroneus longus is a causative factor, and weakness of the anterior tibial has been suggested by several authors. Weakness of the muscles of the calf was advanced as the cause of clawfoot by Barwell (1865) and more recently by Royle (1927). Altakoff (1931) published an article with illustrations of a model to demonstrate his theory that overactivity of the calf muscles causes clawfoot. He stated that after the limit of plantar flexion at the ankle joint is reached the calcaneus is pressed forward, pushing up the head of the talus and allowing the forefoot to be dragged down by the plantar fascia. Hammer toes are then produced by the overacting long toe extensors.

That muscular imbalance is important in the minds of many students of this condition is obvious from the aforementioned references and from the fact that much work is being done in an attempt to show the presence of very slight changes in the power of individual muscles.

This is necessary in order to uphold the theory of muscular imbalance, because by ordinary clinical means no weakness can be demonstrated in a typical clawfoot.

These theories of muscular imbalance are probably rendered untenable by the fact that many feet with definite weakness of muscles or groups of muscles have been observed for long periods without showing clawfoot. For instance, a valgus deformity with slight equinus and forefoot abduction usually follows paralysis of the anterior tibial muscle. A varus deformity without marked cavus follows paralysis of the peroneus longus muscle. Moderate equinus deformity follows paralysis of the long toe extensors. Weakness of the calf muscles, with strong posterior tibial and peroneus longus muscles, yields a deformity resembling clawfoot but lacks its stiffness and hammer toe deformity.

#### PARALYSIS IN THE FOOT FOLLOWING POLIOMYELITIS

Clawfoot associated with other residuals of poliomyelitis is frequent. Shaffer's observation that the deformity develops after the paralysis of the extremity has apparently entirely disappeared, or occurs in the opposite supposedly sound foot, has been confirmed repeatedly. He thought that the condition might be the result of imperfect recovery of power, leaving a slightly disturbed muscular imbalance. He could find no definite loss of power as measured with the faradic current. In discussing the occurrence of clawfoot in the absence of a history of poliomyelitis he said, "There is in none of my cases any history which leads me to think of the spinal cord; on the contrary, the clinical picture points to another motor tract, viz., that of the brain."

Weakness of the intrinsic muscles of the foot due to paralysis from mild unrecognized attacks of poliomyelitis is a favorite theory among orthopedic surgeons and has been discussed under intrinsic muscular imbalance.

Since the epidemic of 1931, 341 cases of poliomyelitis have been followed at the New York Orthopaedic Dispensary and Hospital. In approximately 40 of these the development of clawfoot was observed, occurring after a definite transient paralysis with complete recovery of power as determined by clinical examination. The latent period of its appearance varied from three to twenty-four months. Clawfoot occasionally developed in feet having definite paralysis at the time.

#### DISEASES OF THE CENTRAL NERVOUS SYSTEM

Deformities of the foot follow a great variety of diseases of the nervous system. Typical clawfoot is frequent in Friedreich's ataxia, interstitial hypertrophic neuritis of childhood, neuritic muscular atrophy (the peroneal types of Charcot-Marie-Tooth), spastic paralysis, poliomyelitis and tumor of the spinal cord. Kraus (1922) wrote on the

relation of clawfoot to diseases of the nervous system and listed many conditions in which he had observed an almost identical deformity.

#### HEREDITY

Clawfoot is common among the deformities associated with progressive familial diseases of the central nervous system. Friedreich's ataxia has been traced through several generations by Alpers and Waggoner (1929). Plowright (1928) described a family of eleven children, five of whom had cerebellar disease, and three of these had clawfeet. Clawfoot has been observed frequently with spina bifida and with congenital syphilis. The "idiopathic" type of the deformity is not thought to be inherited.

#### TRAUMA AND INFECTION

Peripheral nerve injury and cicatricial contracture produce deformity of the foot, at times with definite cavus, but a typical clawfoot rarely develops. Isolated cases have been reported following ischemic paralysis, cellulitis or abscess of the sole of the foot and plantar "rheumatism." Sometimes Friedreich's ataxia or another known cause of clawfoot is also present in cases in which a history of injury to the foot is given.

#### EVIDENCE POINTING TOWARD THE CENTRAL NERVOUS SYSTEM AS THE SITE OF THE CAUSATIVE LESION

From the foregoing discussion it will be noted that the known causes of clawfoot, with the possible exceptions of trauma and infection, are lesions of the central nervous system. In various neurologic conditions which frequently produce clawfoot extensive pathologic changes occur in the posterior and lateral columns of the spinal cord, especially in the spinocerebellar tracts and in Clarke's column. These areas are involved regularly in Friedreich's ataxia and often in neuritic muscular atrophy, congenital syphilis, poliomyelitis and interstitial hypertrophic neuritis of childhood (Wechsler 1927). Cerebellar disease has been described with clawfoot (Plowright 1928).

The frequent occurrence of clawfoot after poliomyelitis with no apparent paralysis of the foot suggests that the causative lesion is in the spinal cord and may be similar to that found in the neurologic disorders cited. A study of sections of the spinal cord after poliomyelitis shows that there is extensive damage in addition to destruction of the cells of the anterior horn. It has been reported that death of neurons occurs at the bases of the posterior horns and especially in the cells of Clarke's column (International Committee for the Study of Infantile Paralysis, 1932). There is a remarkable proliferation of connective tissue in the posterior and lateral columns and degeneration of nerve fibers in the

anterior and lateral columns of the white matter. Sections of the spinal cords of monkeys with poliomyelitis in the stage of repair reveal secondary degeneration in the anterolateral and cerebellar tracts and in the posterior columns.

The first report of a microscopic examination in a case of poliomyelitis was that of Cornil in 1863 while in Charcot's service. The patient had poliomyelitis at the age of 2 years and died of cancer forty-seven years later. Cornil found considerable atrophy of the anterolateral bundles of the cord. Nearly a decade later Charcot (1872) commented on the fact that both he and Cornil had completely overlooked the lesions in the motor cells.

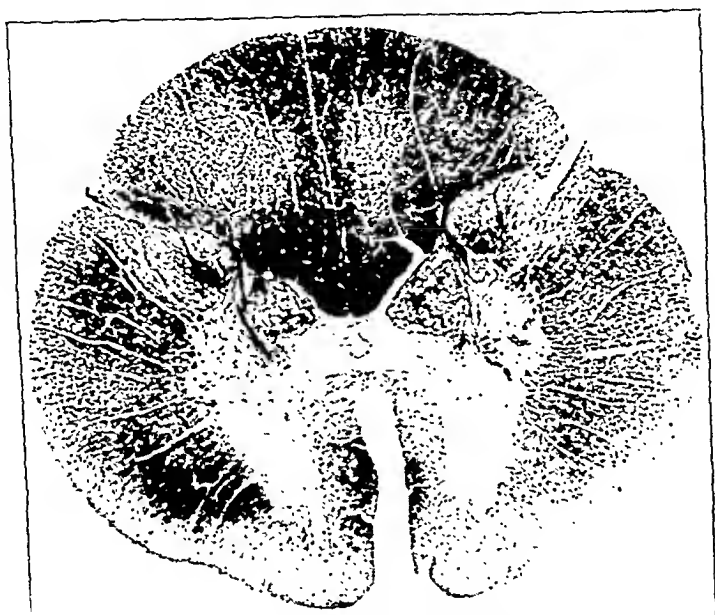


Fig. 1.—Section of the spinal cord of a child aged 1 year and 5 months after an attack of poliomyelitis. The section is stained for myelin by the del Rio Hortega method and shows loss of myelin in the anterior horns and also in the anterolateral columns of the white matter (reproduced from: International Committee for the Study of Infantile Paralysis: Poliomyelitis, 1932).

A rare ataxic type of poliomyelitis has been described with no involvement of the motor nerve cells. The anatomic basis for this condition is established by postmortem observation of involvement of the cerebellum, Clarke's column and the intervertebral ganglions. Howe (1919) stated:

It would appear that the virus of anterior poliomyelitis does not have the peculiar affinity for the nerve elements of the cerebellum which it shows for the motor cells of the cord, and that the symptoms referable to the cerebellum are produced by interference with the function of its connecting nerve tracts and not by the destruction of its inherent nerve elements.



Further evidence of altered function of the spinal cord in poliomyelitis, in addition to the paralysis, is probably to be found in the frequent circulatory disturbance in the skin and in the occurrence of short metatarsal bones (Ferguson 1933). These phenomena are not directly related to the extent of the paralysis.

The function of the cerebellum is not definitely known; however, neurologists agree that it is the great synergizing organ of the central nervous system and that involvement of the spinocerebellar tracts produces a lack of coordination in muscular tone by interrupting the cerebellar reflex arcs. Patients with poliomyelitis and clawfoot rarely show evidence of ataxia, although numerous tests for it have been made. During observation of the development of clawfoot in children with poliomyelitis it was noted that a definite stiffness occurred with no real spasticity before the appearance of structural changes. In Friedreich's ataxia altered muscular tone and deformity occur before atrophy is demonstrable.

Loss of synergetic control of muscular tone is suggested as a possible explanation for the occurrence of clawfoot. The balance of power of muscles acting on the foot is thought to be disturbed so that deformity develops through their altered synergetic action in a way similar to the production of clawfoot in spastic paralysis of childhood or in Friedreich's ataxia. It is realized that in many cases there is no direct evidence of a lesion in the spinal cord and that further investigation will be necessary to establish this theory.

#### PROGNOSIS

Clawfoot of marked degree is disabling and distressingly painful. There is little definite knowledge concerning its rate of development, but it is known to vary markedly. Mills (1924) said that in many cases the deformity is not progressive and advocated conservative treatment. Jones and Lovett (1929) stated that ordinary paralytic clawfoot tends to reach a certain stage and then remain stationary. Observation of cases developing since the epidemic of poliomyelitis in 1931 corroborate these statements. The deformity was found to develop rapidly while the patients were in bed with the feet in plaster boots. It appeared often from two to six months after the acute attack. Progress in these cases was rapid for from two to three months and then became slow. After the primary cause has ceased to act growth of the foot apparently influences the progress of clawfoot by the secondary changes in the bones, muscles and ligaments, but 3 patients with moderate deformity have been observed for over four years during the adolescent period of growth with no increase in the deformity as determined by roentgenograms and clinical examination. On the other hand, in 6 the deformity definitely increased during the same period. They were treated by metatarsal bars and exercises.

When associated with diseases of the central nervous system in which nervous disturbances are continuous and progressive, clawfoot is known to increase steadily until late in adolescence.

The proper selection of measures to allow reestablishment of muscular tone and to correct deformity is necessary for lasting improvement. Relief can be assured in nearly every case by well planned treatment.

#### TREATMENT

The aim in each case should be to relieve symptoms, correct the deformity and prevent recurrence. The trend has been toward more radical procedures even in the milder cases, but every foot is an individual problem and must be treated accordingly. No rigid method can be stated. However, an outline of treatment based on the degree of deformity is suggested.



Fig. 2.—Structural cavus deformity of moderate degree. The site of resection advised is shown by the solid lines.

*Slight Deformity.*—In cases of flexible feet with moderate cavus which disappears on weight bearing special shoes with a low heel and a metatarsal bar should be worn; exercises to increase dorsal flexion and flexibility of the foot and stretching of the toes and muscles of the calf are recommended.

*Moderate Deformity.*—In feet with definite cavus, a loss of flexibility and hammer toes, lengthening of the calcaneus tendon, transplantation of the long toe extensor tendons to the cuneiform bones and arthrodesis of the interphalangeal joint of the first toe are advocated. For a markedly plantar-flexed first metatarsal, transplantation of the extensor hallucis longus tendon to the neck of the first metatarsal and lengthening of the peroneus longus tendon are recommended.

*Marked Deformity.*—In feet with stiff conspicuous cavus on weight bearing and marked hammer toe deformity an anterior tarsal resection,

in addition to the measures enumerated, is advised. Fasciotomy is rarely necessary.

*Severe Deformity.*—In extreme rigid cavus with varus of the heel an anterior tarsal resection is sufficient to correct the deformity in selected cases. If correction of more than 40 degrees is necessary, a subtalar triple arthrodesis is usually a better procedure. It is indicated also with marked calcaneal position of the heel and with lateral instability of the foot. To correct rigid hammer toes it is necessary to perform an arthrodesis of the proximal interphalangeal joints of the toes in addition to transplanting the long toe extensor tendons. At times it is necessary to release the contracted ligaments of the joint capsules.

The procedures suggested for a clawfoot of moderate degree are recommended for the more severe grades in addition to the correction

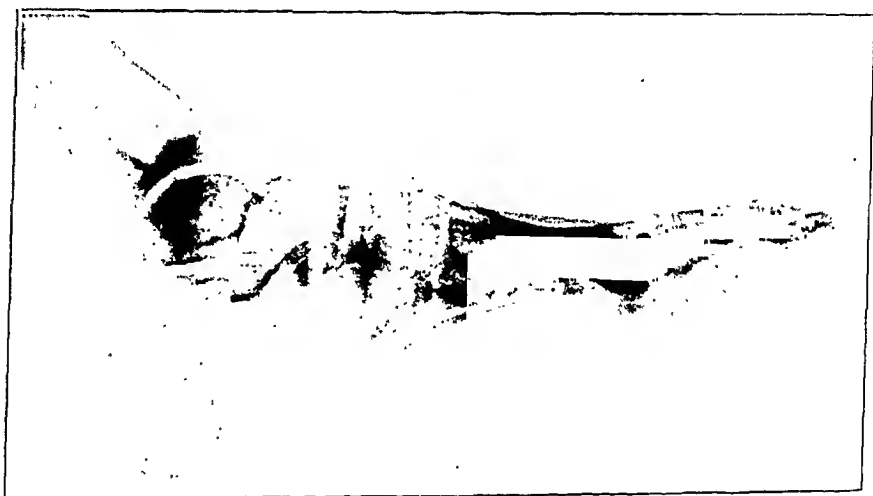


Fig. 3.—Same foot as that shown in figure 2. Anterior tarsal resection has been done with correction of the cavus deformity.

of bony deformity. Forceful wrenching, osteoclasis, etc., are condemned because they produce great trauma and are usually followed by early recurrence of deformity.

In some cases with no equinus deformity correction of the cavus condition by tarsal resection relaxes the long toe extensor tendons sufficiently to allow the toes to lie flat.

The treatment of clawfoot due to Friedreich's ataxia or other progressive diseases of the central nervous system should be the same, or perhaps more radical, because of its progressive and severe nature. The advisability of operating on these patients is questioned by some. The advice of several neurologists consulted is that the patients be kept as active as possible. For this reason it seems worth while to perform what operations are at hand to give these persons comfortable and stable feet.

STUDY OF ONE HUNDRED AND TWO FEET TREATED BY  
ANTERIOR TARSAL RESECTION

In order to determine the results in the treatment of clawfoot by anterior tarsal resection a study was made of the feet on which the operation to correct the cavus deformity was performed between March 14, 1927, and Oct. 21, 1931. Prior to this period resection of bone from the midtarsal region was the procedure used at the New York Orthopaedic Hospital.

For an anterior tarsal resection feet were selected in which the deformity was considered too great to respond to conservative measures or to operation on the soft tissues only. In cavus feet with



Fig. 4.—Structural cavus deformity with slight calcaneus position of the heel. This roentgenogram was taken with the patient standing.

varus deformity or lateral imbalance a subtalar triple arthrodesis was performed, as it was considered a more suitable procedure.

*Surgical Procedure.*—A tourniquet was used. A linear incision was made on the dorsum of the foot from  $\frac{1}{2}$  inch (1.27 cm.) below the center of the ankle joint to the base of the third metatarsal. The vessels were retracted medially. The navicular and cuneiform bones were exposed subperiosteally, and a wedge-shaped resection with the base dorsal was done, including the naviculocuneiform joints and continuing through the central portion of the cuboid. Sufficient bone was removed to allow complete correction of the cavus deformity. Adduction of the forefoot was corrected by widening the resection laterally. The plantar fascia rarely needed to be divided. A plaster boot was worn for six weeks, after which weight bearing was allowed either with or without plaster support, according to the roentgenographic evidence of union.

The anterior tarsal resection alone was done on 52 feet, and on 50 others additional operations were employed to correct hammer toe and equinus deformities.

The long toe extensor tendons were transplanted to the cuneiform bones in 28 of the feet by the method described by Hibbs in 1919. The tendon of the extensor hallucis longus muscle was transplanted into the neck of the first metatarsal in 3 feet. An arthrodesis of the interphalangeal joint of the great toe was always considered advisable when this tendon was transplanted either alone or with the other long toe extensor tendons. If this is not done hyperflexion of the interphalangeal joint is likely to occur and allow pressure areas to develop on the prominent knuckle. Usually the other toes do not require this. The calcaneus tendon was lengthened in 5 feet during the patient's period of hospitalization for the anterior tarsal resection. It was lengthened later in 16 as it was found to be a valuable procedure. The plantar fascia was seldom found tight enough to prevent correction of the cavus deformity by the resection. It was divided 9 times. The medial sesamoid bone of the great toe was later removed from three feet for persistent pain under the first metatarsal head. In 1 foot the

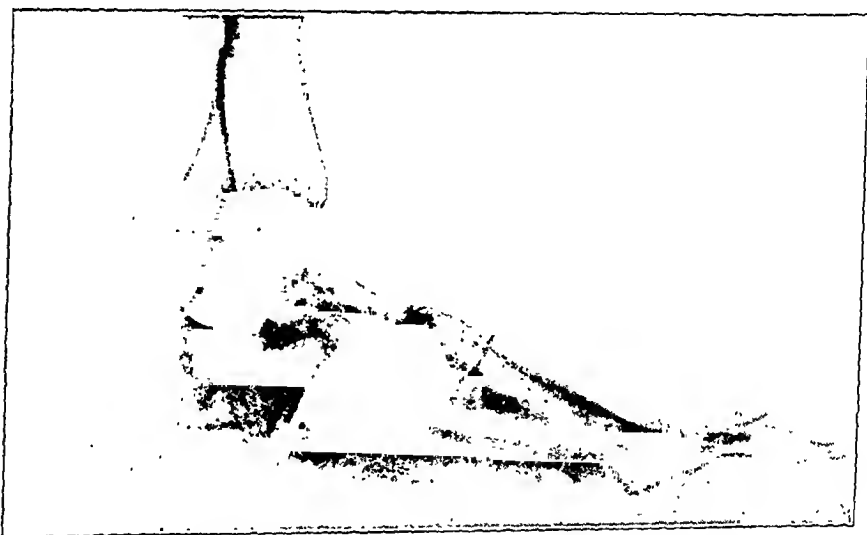


Fig. 5.—Same foot as that shown in figure 4. The structural cavus deformity has been corrected by an anterior tarsal resection. Notice the improved relationship of the calcaneus to the tibia. This roentgenogram was taken with the patient standing.

varus deformity of the heel increased, and a subtalar triple arthrodesis was necessary two years later.

There were 86 patients in this group, including 16 with bilateral deformities, making a total of 102 operations to be studied. Forty-one of the patients were males and 45 females. The diagnosis was clawfoot of unknown etiology in 29 feet, residual of poliomyelitis in 66, spastic paralysis in 5, and Friedreich's ataxia in 2. In some cases the diagnosis was uncertain. The average age at the time of operation was 13.9 years, the youngest patient being 7 years and the oldest 35. Sixty operations were done on the right foot and 42 on the left.

An attempt was made to evaluate the symptoms as reported preoperatively, but since the records were often found to be incomplete and inaccurate no special emphasis is placed on this part of the study. In the large group of patients with poliomyelitis the opposite lower extremity was often extensively paralyzed, and

the attention of both the examiner and the patient was focused on it. Some patients had had operations to correct deformities of the hip or knee which had no direct bearing on the clawfoot. Deformity was the most common symptom. However, 27 patients definitely complained of pain and 40 of easy fatigue. Tender callosities, corns and deformed toes were frequently mentioned. Many complained of stiffness, frequent stumbling and awkwardness, and their parents mentioned the difficulty of finding shoes to fit the patients and spoke of the rapid wear of the shoes.

Definite structural cavus deformity was present in all the feet; it was severe in 43. Dorsal flexion was limited to 95 degrees or more in 72 feet. Varus position of the heel from slight to 15 degrees was noted in 33 feet. Ninety-nine of the feet were described as having a hammer toe deformity. Callosities and corns were distressing in many of them and were noted on examination in 54. The musculature was considered normal in 73 feet. Twenty-nine showed muscular weakness but no lateral instability. External rotation of the tibia was present in 1 case.

In estimating the results of the operation, function, symptoms and correction of deformity were carefully studied. The minimum follow-up period was two years. The results are grouped as follows: excellent, 28; good, 31; fair, 41, and poor, 2.

The results classified as excellent reveal no cavus deformity; the toes are flat in walking; the feet are flexible; there is no limp; there are no tender callosities or corns; dorsal flexion is not limited, and the function is apparently normal, with no ache or pain after strenuous exercise or athletics.

The results classified as good differ from the excellent results only in that slight hammer toe persists; nontender corns or callosities are present, or there is limited dorsal flexion.

The results classified as fair show one or more of the following conditions: slight stiffness or a nonelastic gait, limited dorsal flexion, residual cavus deformity or residual hammer toes. A few patients in this group complain of easy fatigue and of an ache after walking more than one-half mile.

The 2 feet classified as showing poor results are unimproved. One of these was unstable laterally, and a subtalar triple arthrodesis was necessary; the other is unstable laterally, and a subtalar triple arthrodesis is advised.

The follow-up examination revealed that in 27 feet the cavus was incompletely corrected. It was overcorrected in 5, producing flatfoot in 4 cases and a rockerfoot deformity in 1.

Dorsal flexion at the ankle joint was limited to from 95 to 105 degrees in 51 of the feet at the last examination.

Twenty of the 33 feet in which there was varus deformity before operation still retain some of it. Marked varus of the heel was considered a contra-indication for an anterior tarsal resection. However, in feet with marked cavus and slight forefoot adduction with a depressed first metatarsal and slight varus it was expected that the latter would disappear when the cavus and forefoot deformities were corrected.

Residual hammer toe deformity was found in 35 feet. In some of these the toes had remained straight for from six to eighteen months before recurrence.

Callosities and corns were still present in 24 feet. Three patients said that the callosities were worse. In 4 feet they disappeared for from one to two years and then recurred.

The results of the operation in the 29 feet with definite muscular weakness are listed in table 1.

No definite relationship between the age of the patient and the result was noted. Stiffness was more frequently observed in the feet of the older patients but most of them remarked that there was improvement in their gait in addition to the relief from symptoms. A tendency of the deformity to recur was observed to be more frequent in the younger age groups.

In table 2 the results in the group of patients treated by anterior tarsal resection only are compared with results in those having additional procedures.

A study of the 28 feet with excellent results shows that correction of equinus deformity is often necessary. Six feet in this group did not show limitation of dorsal flexion before the operation. In 18 the calcaneus tendon was lengthened. It is interesting that 8 of these feet showed muscular weakness.

TABLE 1.—Results of Operations for the Correction of Muscular Weakness

Muscles	Number of Cases	Results			
		Excellent	Good	Fair	Poor
Normal.....	73	20	24	27	0
Weak.....	29	8	7	12	2
Anterior tibial absent.....	6	0	1	3	2
Anterior tibial weak.....	13	3	4	6	0
Long toe extensors and flexors weak.....	3	2	1	0	0
Peroneal weak.....	4	2	1	1	0
Cliff weak.....	1	0	0	1	0
Flat feet.....	2	1	0	1	0

TABLE 2.—Results of Operations in Patients Treated by Anterior Tarsal Resection Only and in Those Having Additional Procedures

Muscles	Number of Cases	Results			
		Excellent	Good	Fair	Poor
Anterior tarsal resection only.....	52	10	12	29	1
With additional procedures.....	50	18	19	12	1

Seventy-four feet had residual deformity or symptoms and could not be classed as showing excellent results. All but 2 of these, however, were improved. As a result of the follow-up examination it is believed that 51 show equinus deformity which should be corrected and that 37 would be benefited by transplantation of the long toe extensor tendons. In 9 feet with a plantar-flexed first metatarsal transplantation of the extensor hallucis longus tendon to the neck of the first metatarsal would help. In 7 cases the result probably would have been better had a subtalar triple arthrodesis been done because of lateral imbalance in the foot. Five of the feet are too flat and 1 has a markedly relaxed ankle joint.

Observation of these feet leads to the conclusion that symptoms tend to recur if equinus deformity remains. Complete correction by lengthening of the calcaneus tendon is urged so that the foot, when slightly inverted and with the knee straight, can be easily dorsiflexed to 90 degrees. This is especially important when the long toe extensor tendons are transplanted, since it has been found that equinus deformity often progresses after this procedure alone. Persistence of callosities

under the metatarsal heads and recurrence of hammer toe deformity are usually attributable to limited dorsal flexion. Aching feet, stiffness and easy fatigue are apparently often due to the same cause.

In clawfoot of moderate degree better results were often obtained after lengthening of the calcaneus tendon and transplantation of the long toe extensor tendons than after correction of the cavus deformity alone by tarsal resection in the same type of clawfoot. This is thought to be due to the establishment of better balance of muscular tone through the temporary inactivity of the calf muscles induced by the lengthening of the tendon.

*Roentgenographic Observations.*—A study was made of the structural deformity as revealed by roentgenograms. It was found that in a typical clawfoot of marked degree deformity occurs throughout the whole foot and takes place both in the bones and in the joints. The angle between the long axes of the talus and calcaneus averages 46 degrees, which is 6 degrees more than the average angle in a normal foot. In most cases the neck and head of the talus are curved slightly plantarward. The navicular is often definitely wedge-shaped with the base dorsad. The cuneiforms are similarly wedged about as frequently. Slight dorsal bowing of the metatarsals is rare. The first metatarsal is often plantar-flexed at the first cuneiform-metatarsal joint. The degree of cavus deformity was measured on roentgenograms of the foot in the weight bearing position, using the angle between the long axes of the calcaneus and the first metatarsal. This angle averaged 115 degrees preoperatively and 140 degrees after the anterior tarsal resection. Bony union was obtained in all but 2 cases; in these there was a pseudarthrosis between the navicular and first cuneiform bones.

#### CONCLUSIONS AND SUMMARY

Clawfoot is a structural deformity involving the entire tarsus and metatarsus. Hammer toes and contracture of the plantar fascia are thought to be secondary.

Weakness of muscles is not the cause of typical clawfoot.

Evidence is presented suggesting that the etiologic factor is a lesion in the spinal cord which disturbs the synergetic control of muscular tone. Poliomyelitis may be one of the causes of such a lesion.

After an attack of poliomyelitis there is often a rapid development of clawfoot with subsequent slow progress. Many mild cases of deformity can be controlled by conservative measures.

The methods of treatment, which vary according to the degree of deformity, are outlined.

Correction of equinus deformity by lengthening of the calcaneus tendon is strongly advised.

Correction of the structural cavus by anterior tarsal resection is a good procedure. It must frequently be combined with lengthening of the calcaneus tendon and transplantation of the long toe extensor tendons to the cuneiform bones.

The results in 102 clawfeet treated by anterior tarsal resection, with a minimum follow-up period of two years, are as follows: excellent, 28; good, 31; fair, 41, and poor, 2.



## BIBLIOGRAPHY

- Alpers, B. J., and Waggoner, R. W.: Extranural and Neural Anomalies in Friedreich's Ataxia, *Arch. Neurol. & Psychiat.* **21**:47 (Jan.) 1929.
- Altakoff, P.: Zur Analyse des Hohlfußes, *Ztschr. f. orthop. Chir.* **55**:415, 1931.
- Andry, N.: *Orthopaedia*, London, A. Millar, 1743.
- Amundale, T.: *The Malformations, Diseases and Injuries of the Fingers and Toes*, Philadelphia, J. B. Lippincott Company, 1866.
- Astroff, M. S.: Operative Treatment of Pes Excavatus, *Ortop. i travmatol.* **4**:96, 1930.
- Barwell, R.: *On the Cure of Clubfoot Without Cutting Tendons*, ed. 2, London, R. Hardwicke, 1865.
- Bengen: Surgical Treatment of Talipes Cavus, *Verhandl. d. deutsch. orthop. Gesellsch.* **26**:407, 1932.
- Bowen, W. P., and McKenzie, R. T.: *Applied Anatomy and Kinesiology*, ed. 3, Philadelphia, Lea & Febiger, 1923.
- Bréchet, A.: Rôle of Spinal Deformities and Congenital Thickening of Dura Mater in Essential Incontinence of Urine and Hollow Foot, *Rev. méd. franç.* **11**:247, 1930.
- Brockman, E. P.: *Congenital Club-Foot*, New York, William Wood & Company, 1933.
- Camera, U.: Surgical Therapy in Talipes Cavus, *Rev. d'orthop.* **18**:777, 1931.
- Charcot, J. M.: Groupe des myopathies de cause spinale; paralysis infantile, *Rev. phot. d. hôp. de Paris* **4**:36, 1872.
- Cornil, V.: Paralyse infantile; cancer des seins; autopsie; altérations de la moelle épinière, des nerfs, et des muscles; généralisations du cancer, *Compt. rend. Soc. de biol.* **5**:187, 1863.
- Daw, S. W.: Claw Foot, *Clin. J.* **61**:13, 1932.
- Dickson, F. D., and Diveley, R. L.: Operation for Correction of Mild Claw Foot: The Result of Infantile Paralysis, *J. A. M. A.* **87**:1275 (Oct. 16) 1926.
- Duchenne, G. B. A.: *Physiologie des mouvements*, Paris, J. B. Baillière & fils, 1867.
- Duncher, F.: Der Klauenhohlfuß und verwandte progressive Deformitäten als Folgeerscheinungen von Spina bifida occulta, *Ztschr. f. orthop. Chir.* **33**:131, 1913.
- Ferguson, A. B.: Short Metatarsal Bones and Their Relation to Poliomyelitis, *J. Bone & Joint Surg.* **15**:98, 1933.
- Fisher, F. R.: On Paralytic Deformity of the Foot, *Lancet* **1**:142 and 214, 1889.
- Foley, T. M.: Pes Cavus Due to Paralysis of Extensor Muscles, Dorsal Flexors, of the Feet, *South. M. J.* **17**:798, 1924.
- Forbes, A. M.: Claw Foot and How to Relieve It, *Surg., Gynec. & Obst.* **16**:81, 1913.
- Fulton, J. F.: *Muscular Contraction and the Reflex Control of Movement*, Baltimore, Williams & Wilkins Company, 1926.
- Gilroy, E.: Pes Cavus: Clinical Study with Special Reference to Its Etiology, *Edinburgh M. J.* **36**:749, 1929.
- Goff, C. W.: The Pes Cavus of Congenital Syphilis, *J. A. M. A.* **86**:392 (Feb. 6) 1926.
- Pes Cavus of Congenital Syphilis, *Am. J. Surg.* **22**:359, 1933.

- Golding-Bird, C. H.: *Guy's Hosp. Rep.* **41**:439, 1883; quoted by Walsham and Hughes.
- Hackenbroch, M.: *Der Hohlfuss*, Berlin, Julius Springer, 1926.
- Harrison: *Am. J. Anat.* **3**:197, 1904; quoted by Brockman.
- Heyman, C. H.: *The Mobilization of Stiff Metacarpophalangeal Joints*, Surg., Gynec. & Obst. **39**:506, 1924.
- "The Operative Treatment of Claw Foot, *J. Bone & Joint Surg.* **14**:335, 1932.
- Hibbs, R. A.: *An Operation for "Claw-Foot," J. A. M. A.* **73**:1583 (Nov. 22) 1919.
- Hoffman, P.: *An Operation for Severe Grades of Contracted or Claw Toes*, *Am. J. Orthop. Surg.* **9**:441, 1912.
- Howe, M. S.: *The Pathological Changes in the Cerebellum in Acute Anterior Poliomyelitis*, *Neurol. Bull.* **11**:261, 1919.
- International Committee for the Study of Infantile Paralysis: *Poliomyelitis*, Baltimore, Williams & Wilkins Company, 1932.
- Jansen, M.: *Claw Foot*, *Ztschr. f. orthop. Chir.* **58**:193, 1932.
- Jeanne, A.: *Concerning the Plantar Arch in Congenital Pes Cavus with Bony Malformation*, Thèse de Paris, 1897; quoted by Hackenbroch.
- A propos des lésions du pied creux congénital*, *Normandie méd.* **18**:262, 1902.
- Jones, A. Rocyn: *Discussion on Treatment of Pes Cavus*, *Proc. Roy. Soc. Med. (Sect. Orthop.)* **20**:41, 1927.
- Jones, R., and Lovett, R. W.: *Orthopedic Surgery*, ed. 2, New York, William Wood & Company, 1929.
- Kirnisson, E.: *Les difformités acquises de l'appareil locomoteur*, Paris, Masson & Cie, 1902.
- Kochs, J.: *Laminectomy Followed by Spontaneous Correction of Foot Deformity, Accompanying Occult Spina Bifida*, *München. med. Wchnschr.* **74**:1877, 1927.
- Kraus, W. M.: *Relation of the Flexor Adductor Foot Deformity to Diseases of the Nervous System*, *New York State J. Med.* **22**:25, 1922.
- Levick, G. M.: *Action of Intrinsic Muscles of Foot*, *Brit. M. J.* **1**:381, 1921.
- Little, W. J.: *On the Nature and Treatment of the Deformities of the Human Frame*, London, Longmans, Green & Co., 1853.
- Ludloff, K.: *Influence of Posterior Tibial Muscle on Development of Foot Deformities*, *Zentralbl. f. Chir.* **52**:966, 1925.
- Meisenbach, R. O.: *Painful Anterior Arch of the Foot; an Operation for Its Relief by Means of Raising the Arch*, *J. Bone & Joint Surg.* **14**:206, 1916.
- Mills, P.: *Etiology and Treatment of Claw Foot*, *J. Bone & Joint Surg.* **6**:142, 1924.
- Parker and Shattock: *Tr. Path. Soc. London* **35**:423, 1884; quoted by Brockman.
- Parker, C. A.: *Hollow-Foot, Pes Cavus*, *J. A. M. A.* **61**:1886 (Nov. 22) 1913; *Tr. Sect. Orthop. Surg., A. M. A.*, 1913, p. 147.
- Plowright, O.: *Familial Claw-Foot with Absent Tendon Jerks and with Cerebellar Disease*, *Guy's Hosp. Rep.* **78**:314, 1928.
- Pollock, L. J., and Davis, L.: *Peripheral Nerve Injuries*, *Am. J. Surg.* **18**:362, 1932.
- Royle, N. D.: *Claw Foot*, *J. Bone & Joint Surg.* **9**:465, 1927.

- Rugh, J. T.: An Operation for the Correction of Plantar and Adduction Contracture of the Foot Arch, *J. Bone & Joint Surg.* **6**:664, 1924.
- Plantar Fascia: Study of Its Anatomy and of Its Pathology in Talipes Cavus; New Operation for Its Correction, *Am. J. Surg.* **11**:307, 1927.
- Etiology of Cavus and New Operation for Its Correction, *Bull. New York Acad. Med.* **3**:423 (June) 1927.
- Ruiz, E.: Un caso de pie hueco asociado a la espina bifida oculta, *Semana méd.* **11**:306, 1931.
- Scherb, R.: Die transossäre extensorenfixation bei Klauenhohlfuss, *Klin. Wchnschr.* **11**:787, 1924.
- Stauffer, N. M.: Non-Deforming Club Foot with Remarks on Its Pathology, *M. Rec.* **27**:561 (May 23) 1885.
- Sherman, H. M.: Operative Treatment of Pes Cavus, *Am. J. Orthop. Surg.* **11**:374, 1904.
- Sherrington, C. S.: Integrative Action of the Nervous System, New York, Charles Scribner's Sons, 1906.
- Smith, A. D., and von Lackum, H. L.: End-Results of Operation for Claw Foot, *J. A. M. A.* **84**:499 (Feb. 14) 1925.
- Spitzzy, H.: Operative Correction of Claw Foot, *Surg., Gynec. & Obst.* **45**:813, 1927.
- Steindler, A.: Operative Treatment of Pes Cavus, *Surg., Gynec. & Obst.* **24**:612, 1917.
- The Treatment of Pes Cavus, *Arch. Surg.* **2**:325 (March) 1921.
- Stuart, F. W.: Claw Foot—Its Treatment, *J. Bone & Joint Surg.* **6**:360, 1924.
- Tilney, F., and Riley, H. A.: The Form and Function of the Central Nervous System, ed. 2, New York, Paul B. Hoeber, Inc., 1923.
- Tubby, A. H.: Deformities: A Treatise on Orthopedic Surgery, New York, The Macmillan Company, 1896.
- Washam, W. J., and Hughes, W. K.: The Deformities of the Human Foot, New York, William Wood & Company, 1895.
- Wechsler, I. S.: A Textbook of Clinical Neurology, Philadelphia, W. B. Saunders Company, 1927.

# MASSIVE INTRAVENOUS INJECTIONS

## AN EXPERIMENTAL STUDY

HARRY J. WARTHEN, M.D.

RICHMOND, VA.

The injection of blood and of various drugs intravenously is one of the oldest therapeutic procedures that is used in modern medicine.

### HISTORICAL SKETCH

The most complete record of intravenous infusions in the preantiseptic era is found in Fortescue-Brickdale's<sup>1</sup> exhaustive study published thirty years ago. He stated that the earliest recorded transfusion was given to Pope Innocent VIII in 1492. The unfortunate outcome to the recipient and to the donors discredited the procedure, and more than a century elapsed before transfusions were again alluded to, this time by de Colle of Padua in 1628. This was a significant date as Harvey's "*Exercitatio anatomica de motu cordis et sanguinis*" appeared the same year, and the intravenous injection of drugs became a rational procedure. Probably the first experimental infusions were given in 1656 by Christopher Wren (then professor of astronomy at Oxford, but later to achieve fame as England's outstanding architect), who obtained narcosis by injecting a solution of opium into the veins of dogs. These experiments were repeated by Fracassatus of Pisa in 1658.

Gladstone's<sup>2</sup> recent translation of Johann Elsholtz's "*Clysmatica nova*" (Berlin, 1665) indicated that the injection of blood and of various medications intravenously was widely practiced at that time. He termed this method the "new clyster" and observed:

If a tankard of wine is poured into a river, the wine together with the water flows into the sea; in just the same way, whatever liquid is injected into a vein must necessarily reach the heart together with the circulating blood.

Elsholtz in 1661 injected water, Spanish wine, opium and other drugs into the crural veins of dogs. Finding that these infusions gave results similar to those obtained when the drugs were taken by mouth, he injected *aquae plantaginis*, *cardui benedicti* and extract of *cochleariae*

---

This study was aided by a grant from the Valentine Research Fund.

From the surgical departments of the University of Freiburg, Germany, and the Medical College of Virginia.

1. Fortescue-Brickdale, J. M.: A Contribution to the History of the Intravenous Injection of Drugs, *Guy's Hosp. Rep.* **58**:15, 1904.

2. Gladstone, E.: *Clysmatica Nova* (1665) by Johann Sigismund Elsholtz, *California & West. Med.* **38**:432 (June); **39**:45 (July); 119 (Aug.); 190 (Sept.) 1933.

into the veins of three human subjects without ill effects. He reviewed the literature and cited experiments by Fracassatus of Pisa, Lower of Oxford, Dionysius of Paris and Mollerius of Denmark in which infusions and transfusions were given to animals and human beings. The blood of animals was frequently injected into human subjects, and cures were reported in cases of syphilis, epilepsy and intractable fevers after the injection of the blood of calves and of sheep. This form of treatment increased in popularity, and conflicting claims of priority were advanced by individual physicians and by groups of physicians. Elsholtz attempted to reconcile these differences of opinion in the closing passages of his book by stating:

Let the Italians contend with the French about their priority, and the English with the Germans; perhaps they all are right since their ideas about the subject coincide . . . nevertheless, since this question has been aired seriously here and there, it does not seem to me that I am mistaken, or that I am unjust to anyone, if I believe that I first made in suitable quantity and adequate variety the experiments in simple infusion on which this whole discovery depends and that I then first combined these experiments properly, and certainly this is the hinge on which the whole affair turns.

Despite this auspicious beginning and the absence of any mention of unfavorable results, many unrecorded fatalities resulted from reactions and from sepsis. So hazardous was the practice that transfusions were forbidden in several European countries and intravenous therapy fell into disrepute.

After a lapse of about one hundred years, a revival of interest in intravenous injections commenced at the beginning of the nineteenth century, and from 1802 to 1827 a journal devoted entirely to transfusions and infusions was published in Copenhagen. In 1823 Hale of Boston described the injection of a therapeutic dose of castor oil into his own circulation with transient but disagreeable effects. Magendie in the same year reported temporary benefit in four cases of hydrophobia from intravenous injections of 600 cc. of warm water. Hayem in 1855 injected a 0.6 per cent solution of sodium chloride into the veins of patients with cholera. Haford in 1869 reported favorable results following the intravenous injection of solutions of ammonia in patients bitten by poisonous snakes. The frequent outbreaks of cholera during the latter half of the nineteenth century furnished the chief indication for intravenous infusions during the period when Pasteur and Lister's teachings received their first widespread clinical application.

The modern story of intravenous infusion dates from 1891, when Matas<sup>3</sup> reported seven recoveries in nineteen cases of severe shock and hemorrhage following the intravenous administration of from 250 to

3. Matas, R.: A Clinical Report on Intravenous Saline Infusion in the Wards of the New Orleans Charity Hospital from June 1888 to June 1891, *New Orleans M. & S. J.* 9:1 and 81, 1891-1892.

1,500 cc. of isotonic salt solution. He stated that in all cases of circulatory failure intravenous infusion of saline solution results in temporary restoration and that this benefit is permanent in syncope due to simple and uncomplicated hemorrhage. Mayo Robson<sup>4</sup> in 1893 reported a case of severe shock followed by recovery after 2,500 cc. of physiologic solution of sodium chloride was given intravenously. Mummery<sup>5</sup> in the Hunterian Lectures for 1905, stated that intravenously injected saline solution directly combats the fall in blood pressure by diminishing the disproportion between the quantity of circulating fluid and the capacity of the circulatory system, and also diminishes the viscosity of the blood incident to shock. He recommended the use of from 180 to 200 cc. an hour until the blood pressure remains at a safe level.

Because of the danger of overburdening the heart by single large intravenous infusions and the difficulty encountered in finding suitable veins in patients requiring repeated injections, Friedmann<sup>6</sup> in 1912 devised an apparatus, somewhat similar to that used in treatments by rectal drip, through which physiologic solution of sodium chloride could be given intravenously for long periods. A rubber tube connected to a funnel and containing a glass dropper, permitting the regulation of the flow, led to a glass cannula which was inserted into a superficial vein at the bend of the elbow. With this apparatus he was able to inject from 3 to 5 liters of physiologic solution of sodium chloride over a period of twenty-four hours. The amount of fluid needed and the general condition of the patient determined the rapidity with which the fluid was given. Friedmann advised this method chiefly in cases of dehydration, such as cholera, diarrhea, ileus, carcinoma of the stomach, infectious diseases associated with collapse, peritonitis and sepsis. His conclusions, based on twenty cases in which the patient was treated by this method, were that the heart is not overburdened and sudden rises in the blood pressure are avoided, normal kidneys are stimulated to increased activity, the method is relatively free from discomfort, and the treatment may be continued until the condition of the patient improves sufficiently to warrant its discontinuance.

In 1924 Matas<sup>7</sup> reported a series of cases in which a 5 per cent dextrose solution in distilled water was given continuously through a

4. Robson, M.: Severe Shock Treated by Transfusion or Infusion of Normal Saline Solution. *Brit. M. J.* 1:697, 1893.

5. Mummery, J. P. L.: The Physiology and Treatment of Surgical Shock and Collapse. *Lancet* 1:696 (March 18) : 776 (March 25) ; 846 (April 1) 1905.

6. Friedmann, M.: Ueber intravenöse Dauerinfusion, München. med. Wchnschr. 60:1022, 1913.

7. Matas, R.: Continued Intravenous "Drip," with Remarks on the Value of Continued Gastric Drainage and Irrigation by Nasal Intubation with a Gastro-Duodenal Tube (Jutte) in Surgical Practice. *Ann. Surg.* 79:643 (May) 1924.

Murphy drip apparatus and a cannula tied in a vein. Dextrose, which had been used previously as a substitute for salt in subcutaneous infusions, was adopted because of its nutritive and stimulating properties and because of the danger of the retention of sodium chloride in prolonged administration. Matas felt that intestinal obstruction, septic peritonitis, disease of the biliary tract with hepatic insufficiency, advanced pyloric obstruction and surgical lesions of the kidney with threatened anuria are especial indications for the intravenous administration of dextrose. He first used this method in 1911 when the usual methods for the administration of fluid had failed. So impressed was he by the ease of administration and the marked benefit obtained by this method that he recommended broadening its scope to include the treatment of patients who probably would rally under the more commonplace measures.

Palmedo<sup>8</sup> in 1928 reported one hundred and fifty cases in which the patient was treated with continuous intravenous infusion. He regarded this method as an excellent emergency treatment in cases of shock and of hemorrhage and recommended its use in cases of peritonitis, of dehydrated conditions and of ruptured ectopic pregnancy, and as a pre-operative and postoperative measure in cases of prolonged operation on the gastro-intestinal tract. He advocated continuous intravenous infusion of physiologic solution of sodium chloride whenever he would previously have resorted to subcutaneous infusions. Palmedo warned against overburdening the circulatory system with fluids because of possible cardiac damage and considered lesions of the kidney, high blood pressure, bronchitis and pneumonia as contraindications.

Warthen<sup>9</sup> reported a case of intestinal obstruction in 1930, following gastro-enterostomy and two subsequent operations with release of adhesions and entero-enterostomy in which 54,000 cc. of 5 per cent dextrose in physiologic solution of sodium chloride was administered over a period of eighteen days. This solution contained 2,700 Gm. of dextrose, or 10,800 calories, and was the only fluid or nutriment taken during this time. Autopsy revealed the presence of dense adhesions with multiple complete obstructions. There was no evidence of circulatory damage from this prolonged intravenous therapy. Intestinal obstruction, generalized peritonitis and toxemia following extensive burns were thought to be especial indications for its use. This method was invaluable for dehydrated patients when the usual oral, subcutaneous and anal routes of administration were for any reason inadequate to supply the physiologic needs. The author recommended the

8. Palmedo: *Erfahrungen mit der intravenösen Dauertropfinfusion nach Friedemann*, Arch. f. klin. Chir. **153**:734, 1928.

9. Warthen, H. J.: *Continued Intravenous Dextrose*, Internat. S. Digest **10**:3 (July) 1930.

injection of from 125 to 200 cc. of 5 per cent dextrose in physiologic solution of sodium chloride per hour for adults, with the additional administration of hypertonic salt solution in cases of intestinal obstruction to supplement the chlorides in the blood. Dextrose in distilled water was given to patients with nephritis or to those who showed evidence of retention of salt.

Hendon<sup>10</sup> employed the term "venoclysis" to designate this form of therapy and recommended the use of 10 per cent dextrose in isotonic salt solution administered at the rate of 200 cc. an hour. He found this solution of especial value for the vomiting of pregnancy and reported a surprising increase in the red blood cell counts of patients with pernicious anemia after intravenous infusions.

Various combinations of chlorides have been used as solvents to approximate closely the constituents of normal blood serum. Horsley and Horsley<sup>11</sup> in 1931 recommended the use of 5 per cent dextrose in Ringer's solution (0.7 per cent sodium chloride, 0.03 per cent potassium chloride, and 0.025 per cent calcium chloride in distilled water). They found this solution to be of great value when given intravenously during and after extensive operations on the gastro-intestinal tract and in cases of intestinal obstruction. It was also of value in duodenal fistula when large amounts of fluid were lost, in the vomiting of pregnancy, in diarrhea, in dysentery, in toxic goiter and in hyperthyroidism.

Melzner<sup>12</sup> in 1931 recommended a more widespread use of intravenous infusions and regarded physiologic solution of sodium chloride as the solution of choice. He advised that intravenous injections of fluids be made with caution in the presence of myocardial weakness and disease of the kidney.

Hyman and Hirshfeld,<sup>13</sup> in 1933, in addition to the usual indications for intravenous fluids, recommended from 5 per cent to 10 per cent dextrose in physiologic solution of sodium chloride as a vehicle for massive intravenous doses of specific antisera, such as antipneumococcus serum or tetanus antitoxin, in metabolic and toxic conditions, for instance, dehydration in infants, and mercurial poisoning.

Titus and Lightbody<sup>14</sup> stated that overdosage and underdosage have been common faults owing to the fact that the actual therapeutic intra-

10. Hendon, G. A.: Venoclysis, *J. A. M. A.* **95**:1175 (Oct. 18) 1930.

11. Horsley, J. S., and Horsley, G. W.: Continuous Intravenous Injection of Dextrose in Ringer's Solution, *Arch Surg.* **22**:86 (Jan.) 1931.

12. Melzner, E.: Intravenöse Dauertropfinfusion, *München. med. Wchnschr.* **78**:1983 (Nov. 20): 2039 (Nov. 27) 1931.

13. Hyman, H. T., and Hirshfeld, S.: Therapeutics of Intravenous Drip, *J. A. M. A.* **100**:305 (Feb. 4) 1933.

14. Titus, P., and Lightbody, H. D.: Report of Investigations to Determine the Therapeutic Dose of Dextrose Administered Intravenously, *Am. J. Obst. & Gynec.* **18**:208 (Aug.) 1929.



venous dose of dextrose has not been known. They recommended a 25 per cent dextrose solution and suggested that 25 Gm. of dextrose should be given in not less than thirty or thirty-five minutes to an average adult, and limited the therapeutic intravenous dose to 75 Gm. injected over a period of from ninety to one hundred minutes. They felt that less than this amount will not give the maximum therapeutic effect and more than this is likely to produce a reaction from overstimulation of the insulin-producing activity of the pancreas. Because of this they recommended single intravenous doses of dextrose repeated from one to three times daily in preference to prolonged injections, and suggested the possibility that "reactions" during injections of dextrose may be due to hypoglycemia from prolonged overdosage of dextrose causing an overstimulation of the pancreas.

Fatalities following intravenous infusions have occurred. Clark<sup>15</sup> reported three cases in which death followed the injection of small amounts of 10 per cent dextrose and physiologic solution of sodium chloride. These fatal cases were characterized by chills, precordial pain, cyanosis and death in from two to nine hours after the injection. Clark attributed these fatalities to acute cardiac dilatation caused by the overburdening of a supposedly normal heart which had been previously weakened by nervous, operative or toxic trauma.

These references indicate the wide range of conditions in which intravenous infusions may be employed, the gradual increase in the amount of solution that is infused and the present diversity of opinion as to the best solution for intravenous use.

Despite the frequency with which large amounts of dextrose or of salt solution of various concentrations are injected intravenously, little is known about the changes in the blood caused by the addition of these solutions or about the total amount of fluid which can be given by this route without embarrassing the circulatory system. This has been due in part to the fact that the amount of the solution injected has been gradually increased over a period of several decades. Attempts to study the changes in the blood chemistry produced by large intravenous infusions have also been handicapped because the treatment has been used frequently as an emergency measure for acutely ill patients and because of the desire to avoid unnecessary venipunctures in patients requiring subsequent intravenous treatments.

In order to avoid these unfavorable circumstances, at the suggestion of Dr. Dean Lewis, a study of the changes in the blood chemistry following infusions has been made in a series of experimental animals, and varying amounts of solution have been injected to determine the

---

15. Clark, J. H.: Acute Cardiac Dilatation: An Ever Present Danger in Intravenous Injections, *J. A. M. A.* 89:21 (July 2) 1927.

quantity which can be infused without causing death or untoward symptoms.

It has long been known that animals can tolerate large amounts of intravenous fluids. Cohnheim and Lichtheim<sup>16</sup> in 1877 injected a 0.6 per cent solution of sodium chloride in dogs and in rabbits in a study of experimental edema. The fluid was injected by gravity pressure into the jugular vein until the animal died. They found that a rabbit could absorb 46 per cent of its body weight within two hours, and one dog with an opened abdomen received fluid which equaled 92 per cent of its weight before it died. The rabbits as a rule died earlier than the dogs, because of the frequent occurrence of pulmonary edema. The dogs rarely showed this complication and usually died of cardiac weakness or in convulsions. There was less proportional effect on the concentration of the blood with large intravenous infusions than with smaller ones. A moderate increase in the arterial pressure was noted early in the experiments, followed later by a fall in the pressure as the infusions were continued. This may indicate that the total amount of fluid given in these experiments was not a true index of the lethal dose, as a considerable amount of fluid may have been forced into a failing circulation after the animal was obviously moribund. The infusions were accompanied by a steady rise in the venous pressure which increased in proportion to the amount of fluid injected.

Two articles of interest on this subject have recently appeared. Blalock, Beard and Thuss in 1932<sup>17</sup> injected various fluids into the veins of dogs at the rate of 10 cc. per kilogram of body weight per hour. The average duration of the infusion was four hours. They found that 75 per cent of the fluid passed into the serous cavities and tissue spaces. There was no marked alteration in the blood pressure as a result of the infusions.

Miller and Poindexter in 1932<sup>18</sup> injected isotonic sodium chloride solution intravenously and subcutaneously in dogs in an attempt to find a method of determining a deficit or excess of fluid in the body tissues. Although an increase in the volume of circulating blood could not be demonstrated by the vital dye method, the average red cell count and hemoglobin content were decreased more than 20 per cent by the intra-

16. Cohnheim, J., and Lichtheim, L.: Ueber Hydrämie und hydrämisches Oedem, *Virchows Arch. f. path. Anat.* 69:106, 1877.

17. Blalock, A.; Beard, J. W., and Thuss, C.: Intravenous Injections: A Study of the Effects on the Composition of the Blood of the Injection of Various Fluids into Dogs with Normal and Low Blood Pressures, *J. Clin. Investigation* 11:267 (March) 1932.

18. Miller, J. R., and Poindexter, C. A.: The Effects Observed Following the Intravenous and Subcutaneous Administration of Fluid; An Experimental Study on Dogs, *J. Lab. & Clin. Med.* 18:287 (Dec.) 1932.

venous infusions. The total proteins in the blood were decreased, the reduction varying from 20 to 52 per cent with the various injections. The authors were unable to find any index which might serve as a warning against overhydration of tissues, but they stated that the hematocrit is the simplest test for determining the dilution of the blood following the postoperative administration of fluids.

#### EXPERIMENTS

Twenty-one dogs received forty intravenous infusions. Ten infusions were given of each of the four most frequently used solutions, namely 0.7 per cent sodium chloride, 5 per cent dextrose, hypertonic sodium chloride (1.5 per cent and 2 per cent) and 10 per cent dextrose. Twenty-eight infusions were given to ten dogs in the surgical clinic of the University of Freiburg.<sup>19</sup> Owing to the difficulty encountered in obtaining the larger experimental animals in Germany, it was necessary to give several infusions to the same dog. The largest number of intravenous infusions was given to dog 6. This dog received seven injections during a period of three months. Sufficient time was permitted to elapse between each two infusions to allow the dog to recover from the effects of the last injection. Determinations of the blood pressure could not be made in this first series of twenty-eight experiments as the procedure necessitated the ligation of the femoral artery with circulatory changes in the involved extremity. Owing to the difficulty of restraining unanesthetized animals for long periods of time, single massive infusions were given in the space of a few minutes rather than prolonged continuous infusions. Healthy dogs were used in these experiments, but no attempt was made to obtain young animals.

The experiments were performed in the following manner: The weight of the dog was recorded and a preoperative dose of morphine (10 to 20 mg. per kilogram of body weight) was given. The majority of the experiments were performed under local anesthesia in order to approximate normal conditions as nearly as possible. Five animals received ether or diallyl-barbituric acid. An incision was made so as to expose the femoral vein. Fifteen cubic centimeters of blood was withdrawn for chemical analysis, and a cannula or a needle was inserted in the vein through which the solution was infused under gravity pressure. The temperature of the infused solutions was kept at 100 F. At the conclusion of the experiment another sample of blood was withdrawn for chemical determinations.

In the first few infusions only 1,000 cc. of solution was injected over a period of thirty or forty minutes, but this amount was so well tolerated that the infusions were gradually increased until on one occasion 2,600 cc. of fluid was given in twenty-six minutes.

Chemical determinations<sup>20</sup> were made of the blood sugar, nonprotein nitrogen and chlorides, expressed in milligrams per hundred cubic centimeters of blood, before and after each infusion. The resistance of the red blood cells to hemolysis by various hypotonic solutions of sodium chloride was also determined in order

19. Warthen, H. J.: Ueber intravenöse Infusion in grossen Mengen; eine experimentelle Studie, *Beitr. z. klin. Chir.* 159:51 (Jan.) 1934.

20. The nonprotein nitrogen was determined by the Folin and Wu method. The blood sugar was determined by a modification of the Folin and Wu method. The blood chlorides were determined by the Whitehorn method. The blood chlorides are expressed as sodium chloride throughout this paper.

to note any change that occurred following large infusions. The pulse rate was observed, symptoms were noted and the condition of the dog at the conclusion of the experiment was recorded. Determinations of blood pressure were made during twelve infusions. In order to have a standard for comparison, the amount of fluid infused into each dog was calculated in cubic centimeters per kilogram of body weight.

In each of tables 1 to 4 the first seven experiments recorded were performed in Germany and the last three experiments were performed in this country. In order to facilitate a comparison of these two subgroups the average values are given separately in each table. At the bottom of each column a final average is given which includes all of the experiments in the table. Unless otherwise specified, all references to average values refer to the final average.

*Series 1 (Infusion of 0.7 Per Cent Sodium Chloride Solution).*—Six dogs received ten infusions of 0.7 per cent sodium chloride solution in amounts varying from 65 to 175 cc. per kilogram of body weight. The average amount injected was 106 cc. per kilogram of body weight. The average duration of the infusions was thirty minutes.

The average nonprotein nitrogen content of the blood before the infusions was 23.2 mg. per hundred cubic centimeters; after the infusions it was 18.9 mg., showing a decrease of 4.3 mg. The average blood sugar value before the infusion was 128 mg. per hundred cubic centimeters; after the infusions it was 147 mg., showing an increase of 19 mg. The average blood chloride content rose from 633 mg. per hundred cubic centimeters to 709 mg., showing an increase of 76 mg. The resistance test showed a very slight increase in the fragility of the red blood cells following the infusions. Hemolysis began with a concentration of sodium chloride of 0.42 per cent and was complete with a concentration of 0.32 per cent before the infusions, and began with a 0.43 per cent concentration and was complete with a 0.33 per cent concentration after the infusions.

Two dogs in this series voided before the end of the infusion. The pulse rate, which was usually slow at the beginning of the injections as a result of the morphine, increased during the injections, gradually returning to normal after the conclusion of the infusions. No reactions occurred, and the condition of all of the dogs was satisfactory at the conclusion of the experiments. No deaths resulted from the infusions.

*Series 2 (Infusion of 5 Per Cent Dextrose Solution).*—Eight dogs received ten infusions of 5 per cent dextrose solution in amounts varying from 71 to 210 cc. per kilogram of body weight. The average amount injected was 134 cc. per kilogram of body weight. The average duration of the infusions was twenty-four minutes.

The average nonprotein nitrogen content of the blood before the infusions was 29.7 mg. per hundred cubic centimeters; after the infusions it was 22.5 mg., showing a reduction of 7.2 mg. The average blood sugar value before the infusions was 124 mg. per hundred cubic centimeters; after the infusions it was 454 mg., showing an increase of 330 mg. The average blood chloride content diminished from 643 mg. per hundred cubic centimeters to 612 mg., showing a decrease of 31 mg. The resistance test showed a slight increase in the resistance of the red blood cells to hemolysis following the infusions. Hemolysis began with a concentration of sodium chloride of 0.45 per cent and was complete with a concentration of 0.33 per cent before the infusions and began with a 0.44 per cent concentration and was complete with a 0.32 per cent concentration after the infusions.

TABLE 1.—*Infusion of 0.7 Per Cent Sodium Chloride Solution*

Experi- ment No.	Dog No.	Anes- thetic*	Weight, Kg.	Duration, Minutes	Total Amount Given, Cc.	Cc. per Kg. of Body Weight	Nonprotein Nitrogen, Mg. per 100 Cc.		Blood Sugar, Mg. per 100 Cc.		Blood Chlorides, Mg. per 100 Cc.		Fragility of Red Blood Cells†		Comment
							Before	After	Before	After	Before	After	Before	After	
1	3	P	12.5	22	1,000	80	14.0	19.6	163	122	...	...	0.42-0.32	0.42-0.32	Voided once
2	5	P	23.0	40	1,500	65	23.0	16.4	104	92	742	829	0.35-0.20	0.40-0.20	No reaction
3	3	P	12.3	30	1,500	122	17.5	18.2	148	135	590	637	0.44-0.30	0.44-0.30	No reaction
4	6	P	17.0	25	1,750	103	15.1	12.5	151	192	661	754	0.44-0.34	0.40-0.34	No reaction
5	5	P	22.5	30	2,000	88	10.5	16.5	137	141	497	544	0.42-0.32	0.42-0.34	Voided once
6	5	P	20.0	30	2,250	112	33.9	18.5	92	124	819	971	0.40-0.20	0.40-0.32	Slight dyspnea
7	6	P	17.0	40	2,500	147	18.5	6.0	132	117	748	865	0.44-0.32	0.48-0.32	No reaction
Average for first seven dogs			17.7	31	1,785	102	19.7	15.4	124	132	676	771	0.42-0.31	0.43-0.33	
8	11	P	11.3	25	1,500	133	33.8	26.0	153	174	476	570	0.36	0.38	No reaction
9	12	P	15.9	30	950	60	27.0	24.0	146	232	520	612	0.26	0.34	No reaction
10	15	E	14.8	26	2,000	175	34.0	32.0	115	139	544	568	....	....	No reaction
Average for last three dogs			14.0	27	1,633	123	31.6	27.0	140	182	513	583	0.36	0.36	
Average for entire group			16.6	30	1,755	106	23.2	18.9	128	147	633	709	0.42-0.32	0.43-0.33	

\* P represents 2 per cent procaine hydrochloride; E, ether.

† The figures represent the concentrations of sodium chloride with which hemolysis began and was complete.

TABLE 2.—Infusion of 5 Per Cent Dextrose Solution

Experiment No.	Dog No.	Anesthetic*	Weight, Kg.	Duration, Minutes	Total Amount Given, Cc.	Cc. per Kg. of Body Weight	Nonprotein Nitrogen, Mg. per 100 Cc.		Blood Sugar, Mg. per 100 Cc.		Blood Chlorides, Mg. per 100 Cc.		Emglicity of Red Blood Cells†		Comment
							Before	After	Before	After	Before	After	Before	After	
11	2	P	8.7	40	1,000	115	....	....	98	415	...	...	0.46-0.28	0.36-0.20	Voided twice
12	3	P	10.0	20	1,000	100	38.7	11.2	113	551	623	669	0.41-0.34	0.43-0.30	Voided twice
13	1	P	11.0	20	1,000	71	35.8	5.2	...	...	605	715	0.47-0.39	0.55-0.35	No reaction
14	2	P	8.0	25	1,050	131	12.6	5.9	112	408	1,088	754	0.42-0.34	0.40-0.34	No reaction
15	2	P	9.2	25	1,500	163	25.2	14.0	84	184	501	508	0.42 0.28	0.38-0.24	Insulin, 60 units, voided twice
16	7	P	9.5	17	2,000	210	42.0	17.5	170	651	877	994	0.44-0.32	0.40-0.31	Voided once
17	6	P	15.0	24	2,400	160	27.3	18.6	134	551	649	678	0.42-0.32	0.42-0.32	No reaction
Average for first seven dogs							25.3	12.4	149	428	734	720	0.44-0.32	0.43-0.31	
18	16	E	15.2	38	2,000	132	36.4	44.0	105	480	502	332	.....	.....	No reaction
19	17	D	9.4	8	1,200	128	45.0	48.0	102	414	544	342	.....	.....	No reaction†
20	21	P	17.0	13	2,200	120	34.0	38.0	200	426	530	404	0.50-0.31	0.50 0.33	Insulin, 50 units; voided once
Average for last three dogs							38.5	43.3	136	410	510	359	0.50-0.31	0.50 0.36	
Average for entire group							23.7	22.5	124	454	613	612	0.45-0.33	0.44-0.32	

\* P represents 2 per cent procaine hydrochloride; E, ether; D, diethyl-barbituric acid.

† The figures represent the concentrations of sodium chloride with which hemolysis began and was complete.

‡ See text for continuation of infusion in experiment 19.

Five dogs in this series voided before the end of the infusion. One dog vomited during the infusion, probably a result of the preoperative injection of morphine. There was a marked acceleration of the pulse rate during the infusions. No reactions occurred, and the condition of all of the dogs was satisfactory at the conclusion of the experiments. No deaths resulted from the infusions. (See page 217 for a report of the continuation of infusion in experiment 19.)

*Series 3 (Infusion of 1.5 Per Cent and 2 Per Cent Sodium Chloride Solution).*—Seven dogs received eight infusions of a 2 per cent sodium chloride solution and two dogs received a 1.5 per cent solution. The results will be considered together. The smallest amount of solution infused was 60 cc. per kilogram of body weight, the largest was 182 cc. and the average was 112 cc. The average duration of the infusions was twenty-three minutes.

The average nonprotein nitrogen content of the blood before the infusions was 23 mg. per hundred cubic centimeters; after the infusions it was 22.8 mg., showing a decrease of 0.2 mg. The average blood sugar value before the infusions was 161 mg. per hundred cubic centimeters; after the infusions it was 138 mg., showing a decrease of 23 mg. The average blood chloride content rose from 575 mg. per hundred cubic centimeters to 731 mg., showing an increase of 156 mg. The resistance test showed practically no change as a result of the infusions; hemolysis began with a concentration of sodium chloride of 0.44 per cent and was complete with a concentration of 0.34 per cent before the infusions and began with a 0.44 per cent concentration and was complete with a 0.33 per cent concentration after the infusions.

No dog in this series voided before the end of the infusions. The increase in the pulse rate during the infusions was not so marked as was noted during the injections of the other solutions. The dogs in this series showed no reaction to the infusions aside from marked borborygmus during the injection of the solution. The condition of all of the dogs was satisfactory at the conclusion of the experiments, and no deaths resulted from the infusions.

*Series 4 (Infusion of 10 Per Cent Dextrose Solution).*—Nine dogs received ten infusions of 10 per cent dextrose solution in amounts varying from 57 to 189 cc. per kilogram of body weight. The average amount injected was 118 cc. per kilogram of body weight. The average duration of the infusions was twenty minutes.

The average nonprotein nitrogen content of the blood before the infusions was 25.7 mg. per hundred cubic centimeters; following the infusions it was 25.4 mg., showing a reduction of 0.3 mg. The average blood sugar value before the infusions was 158 mg. per hundred cubic centimeters; after the infusions it was 1,018 mg., showing an increase of 860 mg. This marked increase was due chiefly to two large infusions in which the blood sugar value rose to 1,670 and 2,500 mg., respectively. The average blood chloride content diminished from 564 mg. per hundred cubic centimeters to 487 mg., showing a decrease of 77 mg. The resistance test showed a definitely increased resistance to hemolysis following the infusions. Hemolysis began with a concentration of sodium chloride of 0.45 per cent and was complete with a concentration of 0.32 per cent before the infusions and began with a 0.42 per cent concentration and was complete with a 0.29 per cent concentration after the infusions. Insulin in doses varying from 40 to 200 units was given in nine of the ten experiments.

One dog in this series voided before the end of the infusion. The pulse rate increased markedly during the infusions in the majority of the cases, but gradually returned to normal following the injections. Two dogs made convulsive movements during the infusions, and three dogs died within twelve hours as a result of the infusions. (See page 218 for a description of the deaths.)

TABLE 3.—Infusion of 1.5 Per Cent and 2 Per Cent Sodium Chloride \*

Exptl. No.	Dog No.	Age, months	Weight, Kg.	Duration, Minutes	Total Amount Given, Cc.	Cc. of Body Weight	Nonprotein Nitrogen, Mg. per 100 Cc.		Blood Sugar, Mg. per 100 Cc.		Blood Chlorides, Mg. per 100 Cc.		Frugility of Red Blood Cells†		Comment
							Before	After	Before	After	Before	After	Before	After	
21	9	1 <sup>p</sup>	6.8	18	1,000	147	17.2	13.3	172	162	614	678	0.42-0.34	0.42-0.34	No reaction
22	1	1 <sup>p</sup>	10.3	20	1,100	107	21.0	21.0	204	213	561	637	0.44-0.32	0.44-0.30	Borborygmus
23	8	1 <sup>p</sup>	21.0	22	1,500	63	27.6	34.8	163	67	561	661	0.42-0.34	0.42-0.34	Borborygmus
24	6	1 <sup>p</sup>	17.0	18	2,000	118	30.1	22.4	150	114	880	988	0.44-0.31	0.44-0.32	Borborygmus
25	6	1 <sup>p</sup>	15.1	18	2,000	129	16.8	31.9	142	63	529	643	0.40-0.34	0.42-0.32	Borborygmus
26	8	1 <sup>p</sup>	23.0	22	2,000	80	22.1	14.0	158	174	401	601	0.43-0.24	0.40-0.34	Borborygmus
27	8	1 <sup>p</sup>	22.0	15	2,000	91	17.5	21.9	121	117	473	579	0.46-0.32	0.46-0.32	No reaction
Average for first seven dogs							17.2	21.8	150	130	588	602	0.43-0.33	0.43-0.33	
28	13	1 <sup>p</sup>	13.8	20	2,000	145	26.0	21.0	200	160	610	918	0.38	0.36	No reaction
29	14	1 <sup>p</sup>	11.0	30	2,000	182	29.4	28.0	160	125	454	818	0.38	0.38	No reaction
30	12	1 <sup>p</sup>	15.0	32	900	60	23.0	20.0	200	192	508	686	0.50-0.32	0.50-0.30	No reaction
Average for last three dogs							13.3	26.1	187	159	546	817	0.50-0.36	0.50-0.35	
Average for entire group							16.0	23.0	161	138	575	731	0.44-0.34	0.44-0.33	

\* The 1.5 per cent concentration was used in experiments 23 and 24.

† P represents 2 per cent procaine hydrochloride.

‡ The figures represent the concentrations of sodium chloride with which hemolysis began and was complete.



TABLE 4.—*Infusion of 10 Per Cent Dextrose Solution*

Experi- ment No.	Dog No.	Anes- thetic*	Weight, Kg.	Duration, Minutes	Total Amount Given, Cc.	Cc. per Kg. of Body Weight	Nonprotein Nitrogen, Mg. per 100 Cc.		Blood Sugar, Mg. per 100 Cc.		Blood Chlorides, Mg. per 100 Cc.		Fragility of Red Blood Cells†		Comment
							Before	After	Before	After	Before	After	Before	After	
31	9	P	6.7	16	1,000	149	17.9	16.1	191	2,500	614	356	0.33-0.30	0.23-0.24	No reaction; Insulin, 40 units
32	6	P	17.0	45	1,300	76	24.5	17.5	127	804	772	625	0.48-0.36	0.46-0.36	Yolked once; Insulin, 60 units
33	1	P	10.2	20	1,500	148	15.4	6.3	251	430	573	380	0.40-0.28	0.38-0.26	No reaction; Insulin, 100 units
34	6	P	17.5	20	1,500	86	23.8	21.2	124	933	643	310	0.44-0.34	0.42-0.32	No reaction; Insulin, 45 units
35	8	P	26.5	15	1,500	57	32.6	30.1	98	941	690	807	0.44-0.32	0.44-0.34	No reaction; Insulin, 50 units
36	7	P	9.5	15	1,500	189	26.6	24.9	170	1,670	631	1,134	0.42-0.32	0.36-0.22	Died 2 hours later‡
37	10	P	15.5	25	2,000	129	20.3	14.7	110	1,134	298	193	0.48-0.38	0.44-0.32	No reaction; Insulin, 100 units
Average for first seven dogs															
38	19	P	14.7	22	1,514	119	23.0	18.7	153	1,274	603	514	0.43-0.33	0.41-0.29	No reaction; Insulin, 200 units
39	20	F	13.9	20	2,000	144	35.0	44.0	109	346	426	380	.....	.....	Died in 12 hours;‡ Insulin, 200 units
40	22	F	15.0	13	2,400	160	32.8	38.4	240	474	556	366	0.50-0.32	0.46	Died in 12 hours;‡ Insulin, 200 units
Average for last three dogs															
Average for entire group															
			14.6	20	1,700	118	25.7	25.4	158	1,018	564	487	0.50-0.38	0.48-0.28	Died in 12 hours;‡ Insulin, 150 units
													0.45-0.32	0.42-0.29	

\* P represents 2 per cent procaine hydrochloride; F, ether.

† The figures represent the concentrations of sodium chloride with which hemolysis began and was complete.

‡ See text for analysis of deaths.

COMPARISON OF THE SODIUM CHLORIDE VALUES OF THE WHOLE BLOOD AND PLASMA <sup>21</sup>

The sodium chloride content of the whole blood was determined in thirty-eight of the forty experiments and the results of these determinations are given in tables 1 to 4. The sodium chloride content of the plasma was also obtained in eleven of these experiments. A comparison of the sodium chloride values is given in table 5.

TABLE 5.—A Comparison of the Sodium Chloride Values of the Whole Blood and Plasma

Experiment No.	Solution Infused	Amount Infused per Kg. of Body Weight, Cc.	Sodium Chloride, Mg. per 100 Cc.			
			Before		After	
			Whole Blood	Plasma	Whole Blood	Plasma
8	0.7 per cent sodium chloride...	133	476	572	570	606
10	0.7 per cent sodium chloride...	176	544	617	563	643
15	5 per cent dextrose.....	132	562	550	332	342
19	5 per cent dextrose.....	123	544	624	450	422
20	5 per cent dextrose.....	129	536	537	404	421
23	2 per cent sodium chloride....	145	616	520	918	902
29	2 per cent sodium chloride....	152	454	460	543	1,030
30	2 per cent sodium chloride....	60	563	577	636	761
35	10 per cent dextrose.....	144	426	410	350	558
39	10 per cent dextrose.....	160	556	517	366	351
40	10 per cent dextrose.....	137	434	519	322	344
Average.....		139	512	537	531	553

TABLE 6.—Dilution of the Blood After the Infusions

Experiment No.	Solution Infused	Total Amount Infused, Cc.	Estimated Blood Volume of Dog,* Cc.	Duration of Infusion, Minutes	Cell Volume, per Cent		Reduction Following Infusion, per Cent
					Before	After	
9	0.7 per cent sodium chloride	950	1,590	30	61	41	33
10	0.7 per cent sodium chloride	2,600	1,450	26	58	44	24
15	5 per cent dextrose.....	2,000	1,520	25	52	38	27
19	5 per cent dextrose.....	1,200	940	5	44	29	34
	Ringer's solution.....	2,500	(See text)	17	29	17	41
23	5 per cent dextrose.....	2,200	1,700	13	59	45	24
23	2 per cent sodium chloride..	2,000	1,350	30	61	35	43
29	2 per cent sodium chloride..	2,000	1,100	26	50	30	40
30	2 per cent sodium chloride..	900	1,500	32	38	32	16
39	10 per cent dextrose.....	2,400	1,500	13	73	51	30
40	10 per cent dextrose.....	2,000	1,460	12	44	23	25
Average.....		2,075	1,417	26	52	36	32

\* The blood volume was estimated to be one tenth of the body weight.

## DILUTION OF THE BLOOD AFTER THE INFUSIONS

The cell volume <sup>22</sup> expressed in percentage of the total blood volume was determined before and after each of ten infusions.

21. The blood for the determinations of plasma chlorides was collected under oil and centrifugated as for determinations of carbon dioxide in the plasma. Analysis was then made as in the determinations of the chlorides of the whole blood.

22. The cell volume was determined by centrifugating for thirty minutes equal amounts of blood, drawn before and after the infusion, in a graduated centrifuge tube containing an anticoagulant.

Although this series of experiments is small and the conditions as regards the solution injected and the duration of the infusions are so variable that conclusions cannot be drawn, it is noteworthy that the infusion of 2 per cent sodium chloride solution resulted in a greater dilution of the blood than did the injections of the other solutions.

#### CHANGES IN THE PULSE RATE AND IN THE BLOOD PRESSURE

Determinations<sup>23</sup> of the arterial blood pressure were made during twelve intravenous infusions. Three determinations were made with each of the four solutions. The pulse rate and blood pressure were recorded before, during and, when possible, after the infusion. The slower pulse rates and lower blood pressures usually followed the larger preoperative doses of morphine.

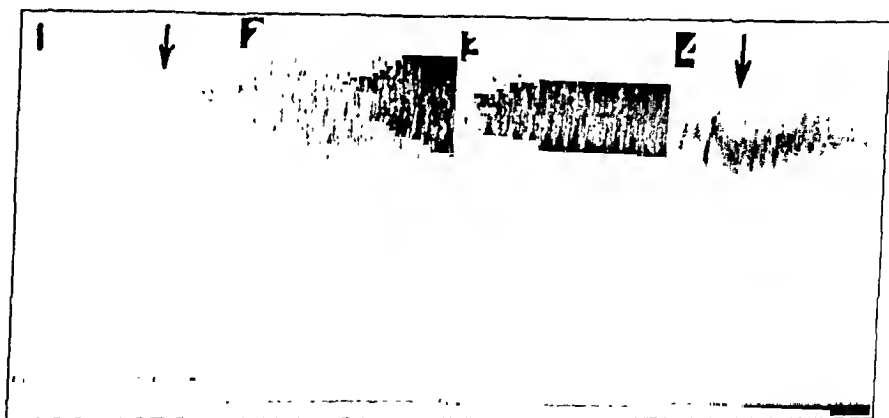


Fig. 1 (experiment 8, dog 11).—Weight, 11.3 Kg.; 1,500 cc. of 0.7 per cent sodium chloride solution (133 cc. per kilogram) injected in twenty-five minutes; no reactions. 1, taken at start of experiment: blood pressure, 90 systolic and 80 diastolic; pulse rate, 120. 2, after eight minutes: blood pressure, 96 systolic and 76 diastolic; pulse rate, 116. 3, after sixteen minutes: blood pressure, 94 systolic and 80 diastolic; pulse rate, 120. 4, at end of experiment (twenty-five minutes): blood pressure, 86 systolic and 70 diastolic; pulse rate, 160. In figures 1 to 12 the arrows indicate the points at which the intravenous injections were begun and discontinued.

The most frequent change noted in the pulse rate was a marked acceleration which appeared as soon as the infusion was begun and continued until the conclusion of the injection. This was most notice-

23. A continuous tracing was obtained by means of a mercury manometer connected to a cannula inserted in the femoral artery. The tracings give an accurate record of the systolic pressure. The diastolic pressure is unusually high in several of the tracings, owing to an instrumental error, with a resulting incorrect pulse pressure. The respiratory excursion was frequently accentuated; at times it simulated that of the pulse pressure.

able when the pulse rate was relatively slow at the beginning of the injection. In experiment 38 the rate increased from 54 to 156 after the injection of 144 cc. of 10 per cent dextrose solution per kilogram of body weight in twenty minutes. When the initial pulse rate was above 100 the increase incident to the infusion was less marked. In only one determination (experiment 19) was there a reduction of the pulse rate during the infusion. This dog received 128 cc. of 5 per cent dextrose solution per kilogram of body weight in eight minutes with a fall in the pulse rate from 130 to 124. Eight minutes later a second infusion of Ringer's solution was begun, and 266 cc. per kilogram of body weight was injected in seventeen minutes, with a final pulse rate of 120.

The systolic blood pressure before the infusions varied from 80 to 150 mm. of mercury. Simultaneously with the beginning of the injection

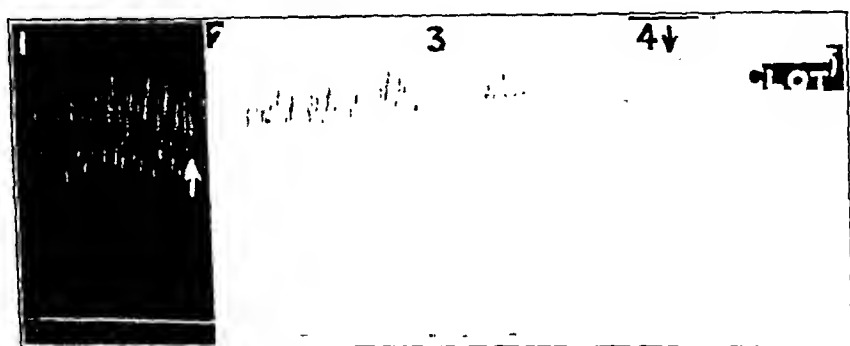


Fig. 2 (experiment 9, dog 12).—Weight, 15.9 Kg.; 950 cc. of 0.7 per cent sodium chloride solution (60 cc. per kilogram) injected in thirty minutes; no reaction. 1, taken at start of experiment: blood pressure, 80 systolic and 56 diastolic; pulse rate, 62. 2, after ten minutes: blood pressure, 80 systolic and 60 diastolic; pulse rate, 70. 3, after twenty minutes: blood pressure, 80 systolic and 70 diastolic; pulse rate, 90. 4, at end of experiment (thirty minutes): blood pressure, 80 systolic.

tion there usually occurred a definite increase in the blood pressure. In the majority of the infusions of 0.7 per cent sodium chloride and of 5 per cent dextrose solution this initial rise was followed by a fall in pressure which continued throughout the remainder of the injection. At the conclusion of the infusions of these two solutions, the pressure had returned to a level approximately the same as the preinjection level or slightly lower. The infusion of hypertonic solutions of sodium chloride and dextrose resulted in a more sustained initial rise, and the pressure following the three infusions of 2 per cent sodium chloride solution was definitely higher than before the injection.

The changes in the venous pressure as a result of the infusions were more constant. Each infusion resulted in engorgement of the veins

which persisted for several hours. Puncture wounds in the walls of the veins bled freely, and it was necessary to ligate the openings in the vessels after blood was withdrawn for the second chemical analysis. In experiment 40 a determination of the venous pressure was made by Dr. J. P. Baker Jr. Following the injection of 137 cc. of 10 per cent dextrose solution per kilogram of body weight in twelve minutes, the venous pressure rose from 50 to 480 mm. of water. The systolic arterial pressure fell from 150 to 136 mm. of mercury during the infusion. Six minutes after the conclusion of the infusion the venous pressure was 560 mm. of water and the arterial pressure was 120 mm. of mercury.

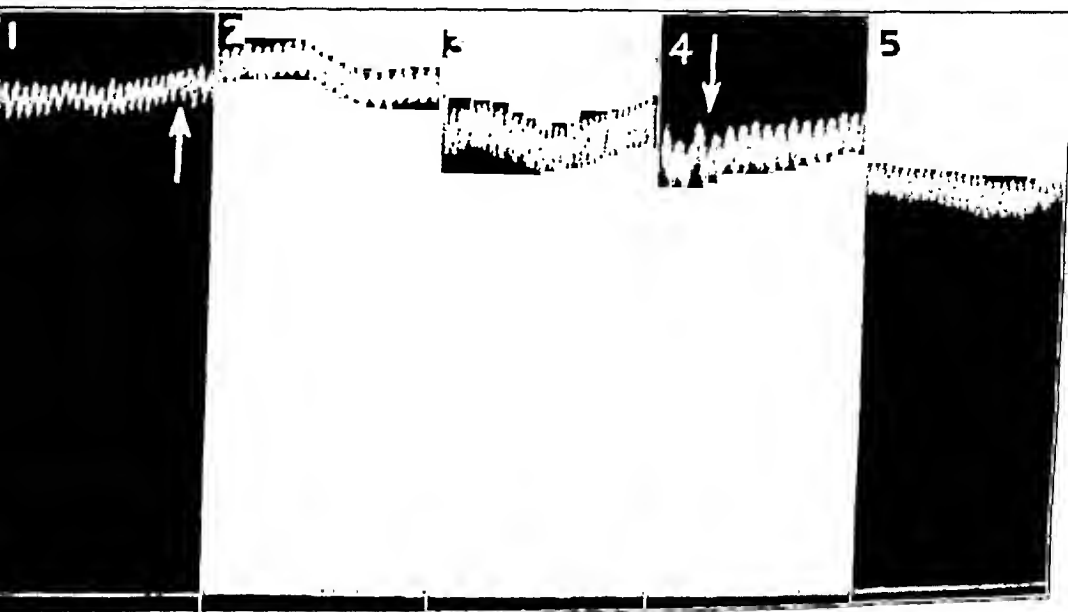


Fig. 3 (experiment 10, dog 15).—Weight, 14.8 Kg.; 2,600 cc. of 0.7 per cent sodium chloride solution (176 cc. per kilogram) injected in twenty-six minutes; no reaction. 1, taken at start of experiment: blood pressure, 140 systolic and 134 diastolic; pulse rate, 124. 2, after nine minutes: blood pressure, 146 systolic and 138 diastolic; pulse rate, 150. 3, after eighteen minutes: blood pressure, 134 systolic and 124 diastolic; pulse rate, 200. 4, at end of experiment (twenty-six minutes): blood pressure, 130 systolic and 120 diastolic; pulse rate, 200. 5, seven minutes later: blood pressure, 116 systolic and 108 diastolic; pulse rate, 200+.

#### RESPONSE TO THE INFUSIONS

The condition of the majority of the dogs at the conclusion of the infusions was satisfactory. All of the animals were obviously larger than at the beginning of the experiment, but, aside from a noticeable clumsiness due to the sudden increase in weight, most of the animals appeared to be unaffected by the infusions. Edema of the subcutaneous

tissues did not appear following any of the infusions. The animals voided freely following the injections. A series of dogs were weighed twelve hours after receiving the injection, and the weight of each animal was found to be less than it had been prior to the infusions.

In one animal pulmonary edema developed. In experiment 19, dog 17 received 1,200 cc. of 5 per cent dextrose solution in eight minutes. The animal was anesthetized with diallyl-barbituric acid. The condition of the dog was satisfactory at the end of the first infusion. After an interval of eight minutes an infusion of Ringer's solution was begun in an attempt to determine the amount of fluid which could be injected before death supervened. The abdomen gradually became distended. This distention increased until respiration became difficult, necessitating

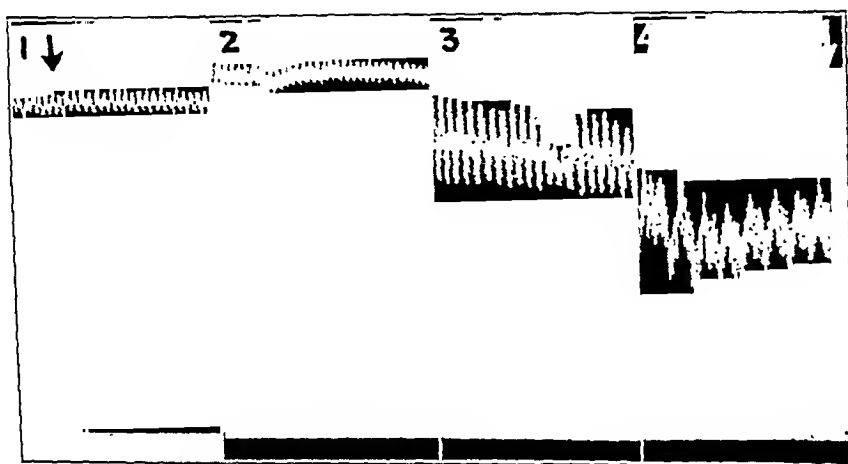


Fig. 4 (experiment 18, dog 16).—Weight, 15.2 Kg.; 2,000 cc. of 5 per cent dextrose solution (132 cc. per kilogram) injected in thirty-eight minutes; no reaction. 1, taken at start of experiment: blood pressure, 110 systolic; pulse rate, 130. 2, after twelve minutes: blood pressure, 120 systolic; pulse rate, 116. 3, after twenty-six minutes: blood pressure, 100 systolic and 90 diastolic; pulse rate, 150. 4, at end of experiment (thirty-eight minutes): blood pressure, 70 systolic and 56 diastolic; pulse rate, 130.

an incision of the abdominal wall to permit the escape of a large amount of free fluid in the peritoneal cavity. When 2,500 cc. of Ringer's solution had been injected, pulmonary edema developed and the infusion was discontinued. In thirty-five minutes 3,700 cc. of fluid, or 394 cc. per kilogram of body weight, had been injected. The condition of the dog did not change and the pulse rate and blood pressure remained relatively constant until the dog was killed fifteen minutes after the end of the second infusion by the intravenous injection of ether. At autopsy the peritoneal cavity was found to contain a large amount of thin fluid.

The gastro-intestinal tract was filled with fluid and its walls were edematous. The lungs were edematous, but there was no free fluid in the pleural or pericardial cavities.

The dogs receiving injections of 5 per cent dextrose and 0.7 per cent or 2 per cent sodium chloride solution were in good condition at the end of the infusion and showed no unfavorable late symptoms referable to the injection.

In two animals cerebral edema developed following infusions of 10 per cent dextrose solution and death resulted within a few hours. A third dog which received 10 per cent dextrose solution also died soon after the injection.

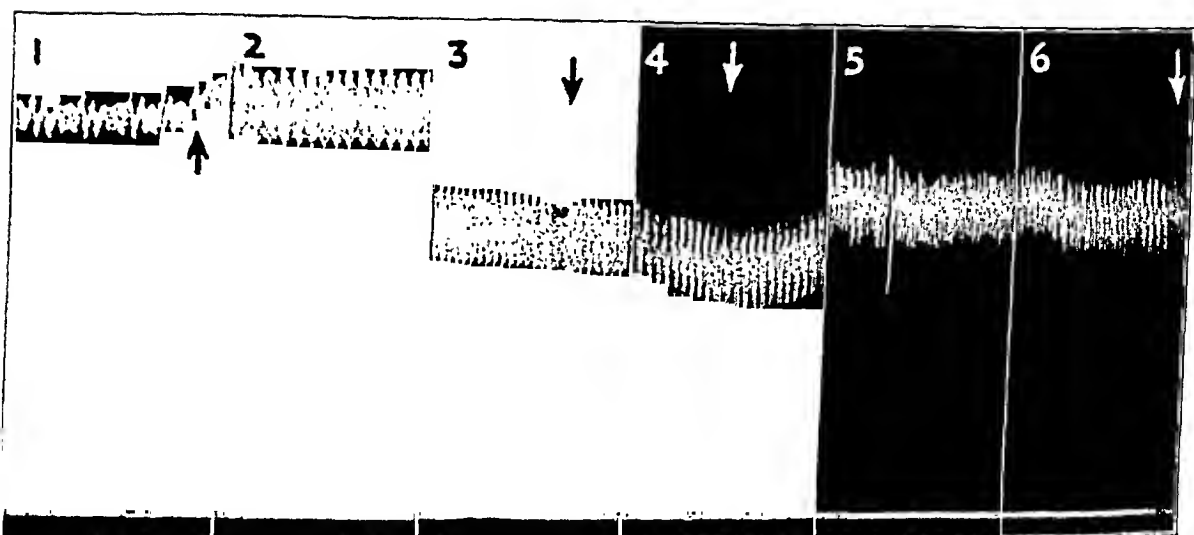


Fig. 5 (experiment 19, dog 17).—Weight, 9.4 Kg. Twelve hundred cubic centimeters of 5 per cent dextrose solution (128 cc. per kilogram) was injected in eight minutes; there was no reaction. After an interval of eight minutes, 2,500 cc. of Ringer's solution (266 cc. per kilogram) was injected in seventeen minutes. Pulmonary edema developed during the latter injection, and the animal was killed fifteen minutes after the end of the second infusion by the intravenous injection of ether. The total amount of fluid, 3,700 cc. (394 cc. per kilogram), was injected in thirty-five minutes. 1, taken at start of experiment: blood pressure, 116 systolic and 106 diastolic; pulse rate, 130. 2, after four minutes: blood pressure, 124 systolic and 104 diastolic; pulse rate, 124. 3, at end of infusion of dextrose solution (eight minutes): blood pressure, 90 systolic and 74 diastolic; pulse rate, 124. 4, eight minutes later, at start of infusion of Ringer's solution: blood pressure, 80 systolic and 64 diastolic; pulse rate, 110. 5, after eight minutes: blood pressure, 96 systolic and 80 diastolic; pulse rate, 124. 6, at end of experiment (seventeen minutes): blood pressure, 90 systolic and 74 diastolic; pulse rate, 120.

#### ANALYSIS OF THE DEATHS

Three dogs died within twelve hours following the injection. These animals received infusions of 10 per cent dextrose solution.

In experiment 36, dog 7 received 1,800 cc. of 10 per cent dextrose solution (189 cc. per kilogram of body weight) in fifteen minutes. Local anesthesia was used. No insulin was given to convert the 180 Gm. of dextrose contained in the solution, and the blood sugar value was

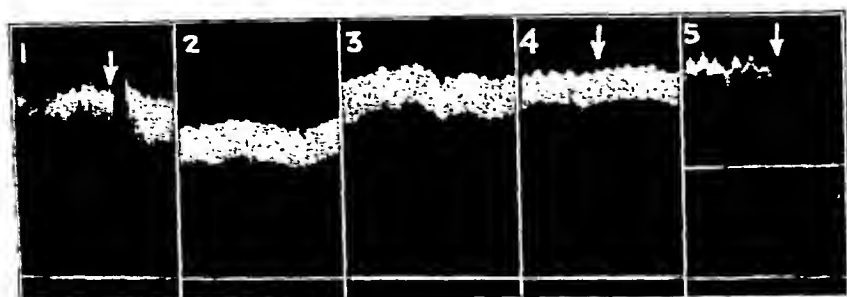


Fig. 6 (experiment 20, dog 21).—Weight, 17 Kg.; 2,200 cc. of 5 per cent dextrose solution (129 cc. per kilogram) injected in thirteen minutes; no reaction. 1, taken at start of experiment: blood pressure, 80 systolic and 70 diastolic; pulse rate, 104. 2, after four minutes: blood pressure, 64 systolic and 52 diastolic; pulse rate, 90. 3, after nine minutes: blood pressure, 82 systolic and 70 diastolic; pulse rate, 116. 4, at end of experiment (thirteen minutes): blood pressure, 84 systolic and 74 diastolic; pulse rate, 104. 5, ten minutes later: blood pressure, 88 systolic; pulse rate, 128.

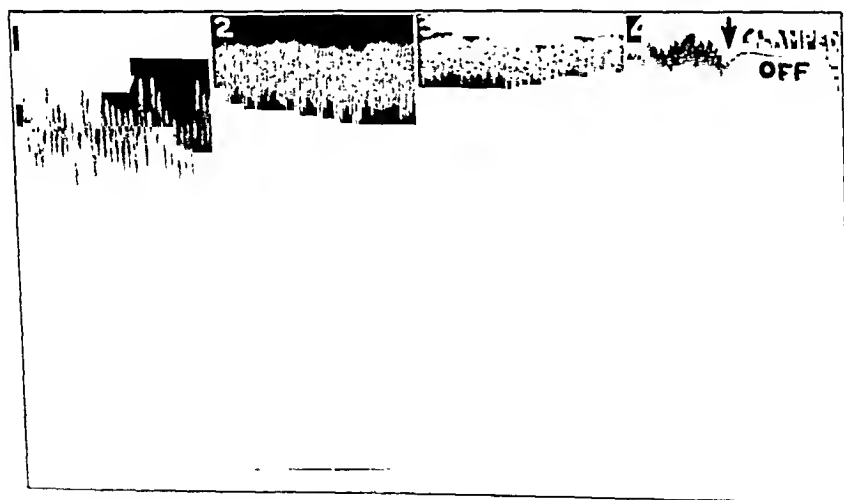


Fig. 7 (experiment 28, dog 13).—Weight, 13.8 Kg.; 2,000 cc. of 2 per cent sodium chloride solution (145 cc. per kilogram) injected in thirty minutes; no reaction. 1, taken at start of experiment: blood pressure, 116 systolic and 96 diastolic; pulse rate, 54. 2, after ten minutes: blood pressure, 138 systolic and 118 diastolic; pulse rate, 104. 3, after twenty minutes: blood pressure, 138 systolic and 128 diastolic; pulse rate, 112. 4, at end of experiment (thirty minutes): blood pressure, 138 systolic and 130 diastolic; pulse rate, 110.



1,670 mg. per hundred cubic centimeters after the injection. After the injection of 1,500 cc. of solution the dog made slight convulsive movements which continued until the end of the injection. At the conclusion of the infusion the respirations suddenly became slow and shallow and the pulse rate increased from 88 to 140 per minute. A series of convulsions followed which continued until the animal died three hours later. At autopsy the stomach was found to be greatly dilated and the lungs were edematous. There was marked edema of the walls of the stomach and the intestine. A small amount of fluid was present in the peritoneal cavity.

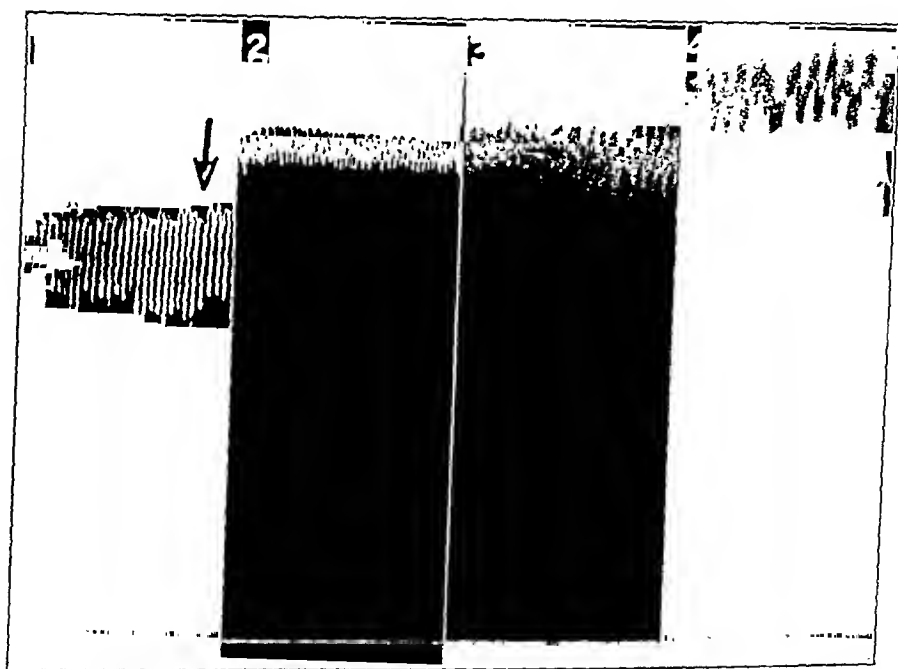


Fig. 8 (experiment 29, dog 14).—Weight, 11 Kg.; 2,000 cc. of 2 per cent sodium chloride solution (182 cc. per kilogram) injected in thirty-six minutes; no reaction. 1, taken at start of experiment: blood pressure, 112 systolic and 88 diastolic; pulse rate, 64. 2, after twelve minutes: blood pressure, 136 systolic and 128 diastolic; pulse rate, 168. 3, after twenty-four minutes: blood pressure, 136 systolic and 126 diastolic; pulse rate, 160. 4, at end of experiment (thirty-six minutes): blood pressure, 154 systolic and 144 diastolic; pulse rate, 164.

In experiment 39, dog 20 received 2,400 cc. of 10 per cent dextrose solution (160 cc. per kilogram of body weight) in thirteen minutes. The dog was anesthetized with ether. Two hundred units of insulin was given to convert the 240 Gm. of dextrose contained in the solution. The blood sugar value, which was 240 mg. per hundred cubic centimeters at the beginning of the infusion, rose to 474 mg. at the end of the injection. The dog made several convulsive movements during the

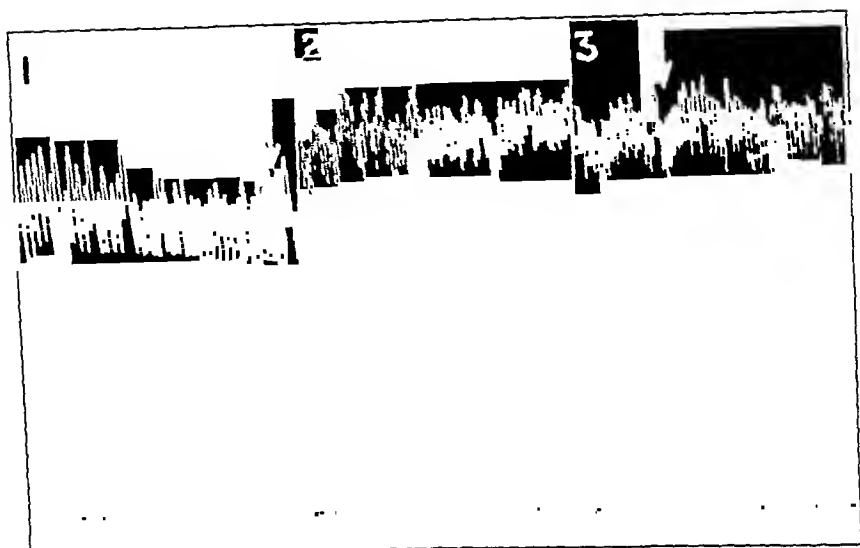


Fig. 9 (experiment 30, dog 12b).—Weight, 15 Kg.; 900 cc. of 2 per cent sodium chloride solution (60 cc. per kilogram) injected in thirty-two minutes; no reaction. 1, taken at start of experiment: blood pressure, 94 systolic and 76 diastolic; pulse rate, 50. 2, after sixteen minutes: blood pressure, 114 systolic and 100 diastolic; pulse rate, 110. 3, at end of experiment (thirty-two minutes): blood pressure, 116 systolic and 100 diastolic; pulse rate, 88.

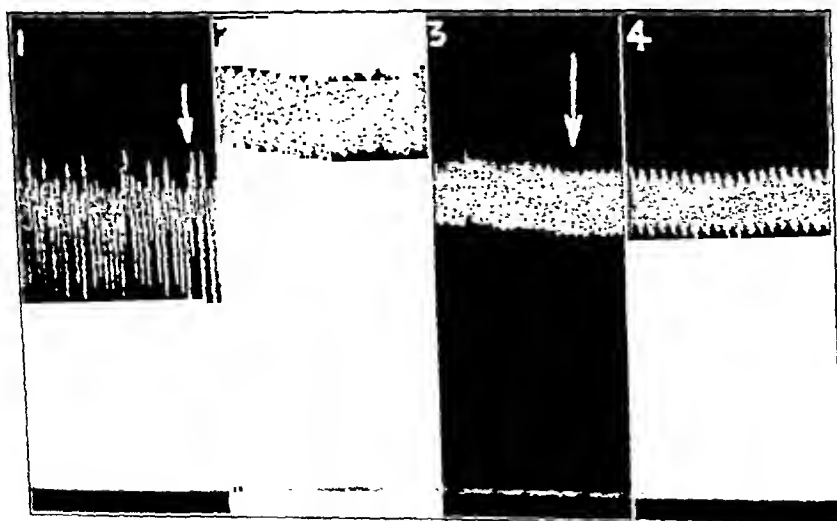


Fig. 10 (experiment 38, dog 19).—Weight, 13.9 Kg.; 2,000 cc. of 10 per cent dextrose solution (144 cc. per kilogram) injected in twenty minutes; no reaction. 1, taken at start of experiment: blood pressure, 104 systolic and 78 diastolic; pulse rate, 54. 2, after ten minutes: blood pressure, 136 systolic and 112 diastolic; pulse rate, 160. 3, at end of experiment (twenty minutes): blood pressure, 106 systolic and 86 diastolic; pulse rate, 156. 4, fifteen minutes later: blood pressure, 104 systolic and 88 diastolic; pulse rate, 142.

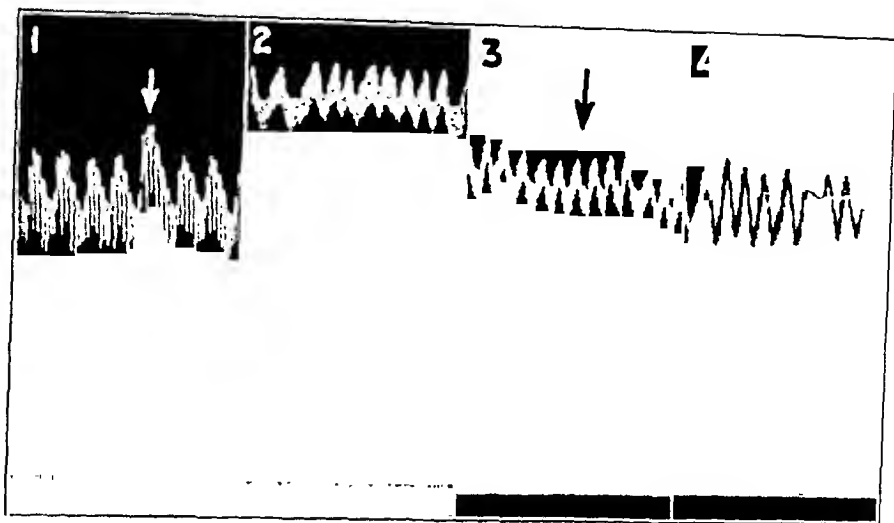


Fig. 11 (experiment 39, dog 20).—Weight, 15 Kg.; 2,400 cc. of 10 per cent dextrose solution (160 cc. per kilogram) injected in thirteen minutes; convulsive twitching during infusion; death within twelve hours. 1, taken at start of experiment: blood pressure, 90 systolic and 74 diastolic; pulse rate, 86. 2, after six minutes: blood pressure, 120 systolic; pulse rate, 134. 3, at end of experiment (thirteen minutes): blood pressure, 92 systolic; pulse rate, 150. 4, six minutes later: blood pressure, 90 systolic; pulse rate, 150.

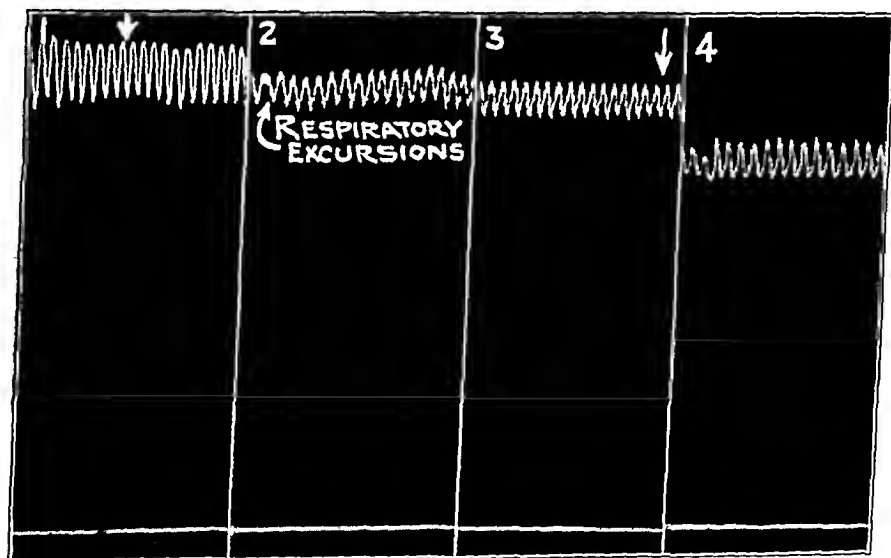


Fig. 12 (experiment 40, dog 22).—Weight, 14.6 Kg.; 2,000 cc. of 10 per cent dextrose solution (137 cc. per kilogram) injected in twelve minutes; marked hemorrhage during experiment; no reaction; death within twelve hours. 1, taken at start of experiment: blood pressure, 150 systolic; pulse rate,  $120 \pm$ ; venous pressure, 5. 2, after six minutes: blood pressure, 140 systolic; pulse rate, 154; venous pressure, 44. 3, at end of experiment (twelve minutes): blood pressure, 136 systolic; pulse rate,  $160 \pm$ ; venous pressure,  $48 \pm$ . 4, six minutes later: blood pressure, 120 systolic; pulse rate,  $150 \pm$ ; venous pressure, 56.

infusion but appeared in good condition at the conclusion. The animal reacted from the anesthetic and vomited a large amount of thin fluid. Several hours after the infusion the condition of the dog appeared to be satisfactory, but death occurred during the following night.

In experiment 40, dog 22 received 2,000 cc. of 10 per cent dextrose solution (137 cc. per kilogram of body weight) in twelve minutes. The dog was anesthetized with ether. One hundred and fifty units of insulin was given to convert the 200 Gm. of dextrose contained in the solution. The blood sugar value rose from 159 to 436 mg. per hundred cubic centimeters. The dog lost a larger amount of blood than was usual during the infusion as a result of the manipulations incident to the determination of the arterial and venous pressure. The systolic blood pressure fell from 150 to 120 mm. of mercury during the infusion. The general condition of the animal appeared satisfactory several hours after the infusion, but death occurred during the following night.

#### SUMMARY

Four series of ten experiments each were made in which twenty-one dogs received intravenous infusions of 0.7 per cent sodium chloride, 5 per cent dextrose, hypertonic sodium chloride and 10 per cent dextrose solutions.

The amount of fluid injected varied from 57 to 394 cc. per kilogram of body weight. The average amount injected for the entire study was 124 cc. per kilogram of body weight. The average duration of the infusions was twenty-four minutes.

The average nonprotein nitrogen content of the blood diminished 7.2 mg. per hundred cubic centimeters following the infusions of 5 per cent dextrose solution, 4.3 mg. following those of 0.7 per cent sodium chloride solution, 0.3 mg. following those of 10 per cent dextrose solution and 0.2 mg. following those of hypertonic sodium chloride solution.

The average blood sugar value increased 19 mg. per hundred cubic centimeters following infusions of 0.7 per cent sodium chloride solution and diminished 23 mg. following infusions of hypertonic sodium chloride solution. The blood sugar value increased markedly following infusions of both 5 and 10 per cent dextrose solution.

The average blood chloride content increased 76 mg. per hundred cubic centimeters following infusions of 0.7 per cent sodium chloride solution and 156 mg. following infusions of hypertonic sodium chloride solution. The average blood chloride content diminished 31 mg. per hundred cubic centimeters following infusions of 5 per cent dextrose solution and 77 mg. following infusions of 10 per cent dextrose solution.

The resistance of the red blood cells to hemolysis was slightly increased following infusions of 5 and 10 per cent dextrose solution;

the resistance was practically unchanged after infusions of hypertonic sodium chloride solution, and there was a slight increase in fragility after infusions of 0.7 per cent sodium chloride solution.

A comparison of the sodium chloride values of the plasma and of the whole blood before and after eleven infusions was not remarkable. The average sodium chloride value of the whole blood before the infusions was 512 mg. per hundred cubic centimeters; after the infusions it was 537 mg., showing an increase of 25 mg. The average sodium chloride value of the plasma before the infusions was 531 mg. per hundred cubic centimeters; after the infusions, it was 583 mg., showing an increase of 52 mg.

Ten dogs with an average estimated blood volume of 1,417 cc. received infusions averaging 2,075 cc. in volume. The average dilution of the blood following the infusions was 32 per cent.

A marked acceleration of the pulse rate occurred during the infusions. The rate gradually returned to normal after the conclusion of the infusions.

A definite rise in the arterial pressure was noted at the onset of the infusions. This initial rise was usually followed by a fall which continued throughout the remainder of the infusion. The secondary fall in pressure was less marked following infusions of hypertonic solutions. After injections of 2 per cent sodium chloride solution the final blood pressure values were higher than at the beginning of the infusions. The venous pressure was markedly increased throughout the infusions.

Pulmonary edema developed in one dog after it had received 394 cc. of fluid per kilogram of body weight in thirty-five minutes.

No dog died following infusions of 0.7 per cent sodium chloride, 5 per cent dextrose or hypertonic sodium chloride solution.

Three dogs died (a mortality of 30 per cent) following injections of 10 per cent dextrose solution. Two of these animals showed signs of cerebral edema; the third lost a large amount of blood during the experiment.

Autopsies on dogs dying after large infusions showed increased fluid in the peritoneal cavity and in the gastro-intestinal tract and edema of the wall of the stomach and the intestine. No fluid was present in the pericardial or pleural cavity. Edema of the lungs was present in two dogs.

#### COMMENT

The first seven experiments recorded in tables 1 to 4, inclusive, were performed in Germany. The three remaining experiments recorded in each of these tables were performed in this country. A comparison of the nonprotein nitrogen and of the chloride values of the blood in these two groups of dogs should be made. The preinjection nonprotein

nitrogen was uniformly lower in the first than in the second group. The preinjection blood chloride values were uniformly higher in the first than in the second group. These differences were present in each of the four series of experiments in this study.

The changes in the nonprotein nitrogen following the injection of the various solutions in these two groups are as striking as the original differences in the nonprotein nitrogen values. In the first group of dogs with a low nonprotein nitrogen value at the onset, the injection of 5 per cent dextrose solution caused the greatest reduction of the nonprotein nitrogen. In the second group of dogs, with a high nonprotein nitrogen value at the onset, the injection of 5 per cent dextrose solution caused the greatest increase in the nonprotein nitrogen. This reversal of results in the two groups also occurred following the injection of 10 per cent dextrose solution. In the first group of dogs the injection of hypertonic sodium chloride solution resulted in a slight increase in the nonprotein nitrogen. In the second group the injection of hypertonic sodium chloride solution resulted in a decrease in the nonprotein nitrogen. Following only the injection of 0.7 per cent sodium chloride solution were the results in agreement; in both groups the injection of 0.7 per cent sodium chloride solution resulted in a moderate reduction of the nonprotein nitrogen.

A ready explanation for this striking difference is not apparent. A possible explanation is found in the differences in the diet of these two groups of dogs. The diet of the German dogs consisted largely of carbohydrates with little protein. The experiments in this country were performed on dogs accustomed to a diet high in proteins and low in carbohydrates. The high protein diet in the second group may explain the higher preinjection nonprotein nitrogen values and may have resulted in an accumulation of nitrogenous substances in the tissues which appeared in the blood following the increased metabolism caused by the injections of dextrose. The failure of these nitrogenous substances to appear in the blood after the injections of sodium chloride solutions may be due in the same manner to the absence of metabolic activity after the infusion of relatively inert solutions.

The chief difference in the effect of the infusions on the blood chloride values in the two groups was noted following the injection of hypertonic sodium chloride solutions. In the first group of dogs with higher preinjection blood chloride values the infusion of a hypertonic sodium chloride solution resulted in a moderate increase in the chloride values. In the second group with a lower preinjection blood chloride value the infusion of a hypertonic sodium chloride solution resulted in a much greater increase in the blood chloride values. This is in accord with the clinical findings in patients with normal and lowered blood chloride values following the injection of hypertonic salt solution.

A larger amount of fluid proportionately was given in each infusion than would be injected intravenously into a human subject. If the injection of 1,000 cc. of fluid an hour is considered the maximum dose for an adult human being weighing 65 Kg., the average amount of solution injected in this study was equivalent to 8 liters of fluid in twenty-five minutes, or twenty times the amount which would be injected into a human subject in a corresponding time. The largest infusion given in this series without causing untoward symptoms was equivalent to 14 liters of fluid for a human being, or about fifty times the amount of solution which would be injected in a corresponding time. In order to produce pulmonary edema in a dog it was necessary to inject the equivalent of 25 liters of fluid for a human being in thirty-five minutes.

While no dog in this study showed evidence of cardiac embarrassment, it must be remembered that these experiments were performed on healthy animals with normal cardiovascular systems. In actual practice intravenous fluids are frequently needed by debilitated patients with damaged circulatory systems. The purpose of the experiments was to determine the margin of safety attending the intravenous injection of fluids and the changes in the blood which follow the injection of these solutions. The results of these experiments should not be interpreted as justifying the injection of larger amounts of fluid than are given at the present time.

#### CONCLUSIONS

1. Large amounts of the usual solutions used for infusions may be injected intravenously into dogs without causing death or evidence of cardiac embarrassment. Injections of excessive amounts of fluid result in cerebral or pulmonary edema.
2. The most favorable changes in the blood chemistry occur with infusions of isotonic solutions of dextrose and sodium chloride. A 5 per cent solution of dextrose causes slightly more desirable changes than does a 0.7 per cent solution of sodium chloride. Injections of hypertonic solutions of dextrose and sodium chloride cause distinctly unfavorable changes in the blood chemistry.
3. The blood sugar value increases following infusions of 0.7 per cent sodium chloride solution and decreases following infusions of hypertonic sodium chloride solution.
4. Large infusions of dextrose and of sodium chloride solutions cause little if any change in the fragility of the red blood cells.
5. There is a marked acceleration of the pulse rate during intravenous infusions.

6. The injection of fluids intravenously results in an initial rise in the arterial blood pressure. This is followed by a secondary fall to, or slightly below, the preinjection level during infusions of isotonic solutions. This secondary fall is diminished or absent during infusions of hypertonic solutions.

7. There is a marked increase in the venous pressure during large intravenous infusions.

8. Diuresis is most marked following infusions of 5 per cent dextrose solution.

9. Edema of the subcutaneous tissues does not occur following the rapid injection of large amounts of fluid intravenously. Edema of the wall of the stomach and of the intestine associated with fluid in the gastro-intestinal tract and in the peritoneal cavity does occur following large intravenous infusions.

10. The intravenous injection of 10 per cent dextrose solution results in frequent fatalities in dogs.

The historical references were obtained from articles by Fortescue-Brickdale<sup>1</sup> and Gladstone.<sup>2</sup>

Drs. E. Rehn and H. Widenhorn of Freiburg and Drs. I. A. Bigger, J. C. Forbes, H. B. Haag and C. M. Nelson of Richmond assisted in this study.



# PRIMARY ISOLATED LYMPHOGRANULOMATOSIS OF THE STOMACH

## REPORT OF A CASE

HARRY N. COMANDO, M.D.

NEWARK, N. J.

Reports of cases of primary isolated Hodgkin's disease of the stomach are sufficiently rare in the literature to warrant the report of another case. Since the time of Billroth, Hodgkin's disease has been definitely placed in the category of medical diseases. The reason that this disease has come to be considered nonsurgical is not so much the technical surgical difficulties entailed as the unfavorable end-results that have followed operative treatment. However, Singer,<sup>1</sup> in a splendid article in 1931, after a careful résumé of the entire literature, cited sufficient evidence to challenge this conception of the disease when the pathologic process is limited to the gastro-intestinal tract. In his article he cited the reports of six cases which he had found in the literature and added one case of his own. A careful search of the literature from 1931 to the present time has failed to disclose any additional cases. At this time I should like to report another authentic case which fully bears out Singer's contention as to the operability and prognosis in such cases.

## REPORT OF CASE

*History.*—Mr. J. S., German, aged 27, was first seen on April 26 1930. For the past three years he had had pain in the epigastrium beginning about three or four hours after meals. The pain was dull, was not relieved by food and radiated to the left side of the chest and to the back. Immediately after eating his abdomen became distended, he belched a great deal, and sometimes vomited. The vomitus consisted of food that had been eaten recently and never contained any blood. The stools had not been bloody. His bowels always moved satisfactorily. His appetite and general health and strength were apparently good. He had lost 15 pounds (7.5 Kg.) during the past year.

*Examination.*—Physical Examination: The patient was a young man about 5 feet and 7 inches (170 cm.) in height, weighing 120 pounds (54.4 Kg.). His chest, abdomen and extremities were essentially normal. The Wassermann and the Kahn test were negative. Examination of the blood showed 4,550,000 erythrocytes, 80 per cent hemoglobin, 6,500 leukocytes, 60 per cent polymorphonuclears,

---

From the Surgical Service of Dr. Harry N. Comando, Newark Beth Israel Hospital.

1. Singer, Harry A.: Primary Isolated Lymphogranulomatosis of the Stomach, Arch. Surg. 22:1001 (June) 1931.



Fig. 1.—Roentgenogram of the stomach in upright position, showing the characteristic filling defect in malignant infiltration of the pyloric portion of the stomach. The walls of the pylorus are rigid and irregular, and the lumen is narrowed.



Fig. 2.—Roentgenogram of the stomach in horizontal position, showing infiltration of the pyloric portion.

37 per cent lymphocytes, 1 per cent eosinophils, 1 per cent basophils and 1 per cent endothelial cells. The urine was normal except for a faint trace of albumin.

Roentgen Examination (Dr. Nathan James Furst): Examination of the gastro-intestinal tract after the ingestion of a contrast meal showed a medium-

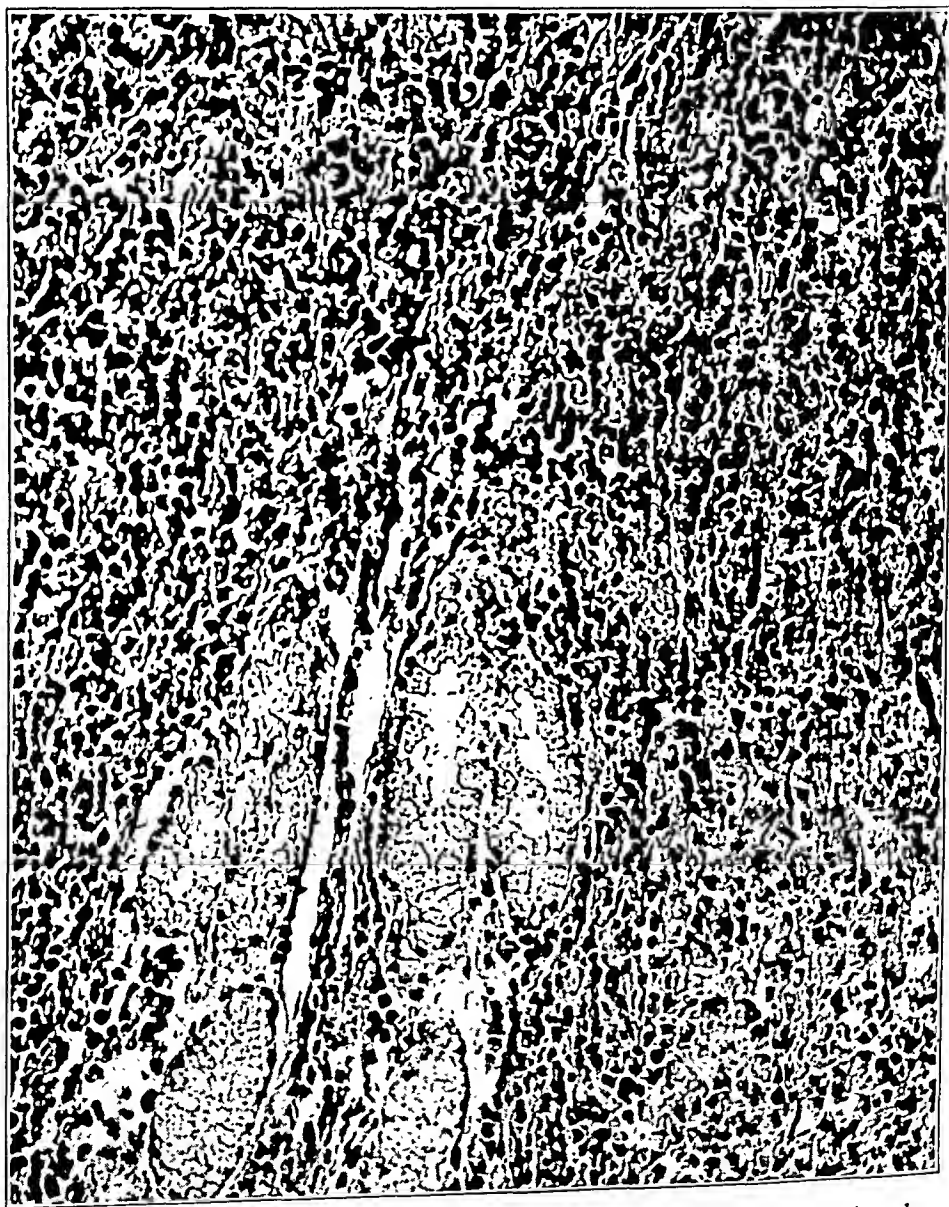


Fig. 3.—Hodgkin's disease (gastric type). Photomicrograph showing lymphogranuloma of the submucosa;  $\times 150$ .

sized, hypertonic stomach that was active in tone. Its axis was oblique to the lowest point of the greater curvature and about 1 inch (2.5 cm.) below the anterior intersuperior spinous line. The pylorus was situated to the right of the midline and on a level with the fourth lumbar vertebra. Gastric mobility was only fair.

No defect in the pars cardia was noted. In the distal part of the pars media and in a portion of the pylorus a narrowed region was noted for a distance of about 1 inch. The bulbus duodeni was inclined to spasm.

Peristalsis was sluggish. At the point of canalization, no peristalsis was visible. Evacuation was delayed. A small gastric residue remained after six hours, the head of the contrast meal having reached the ascending colon. A tendency to colonic hypermotility was also noted.

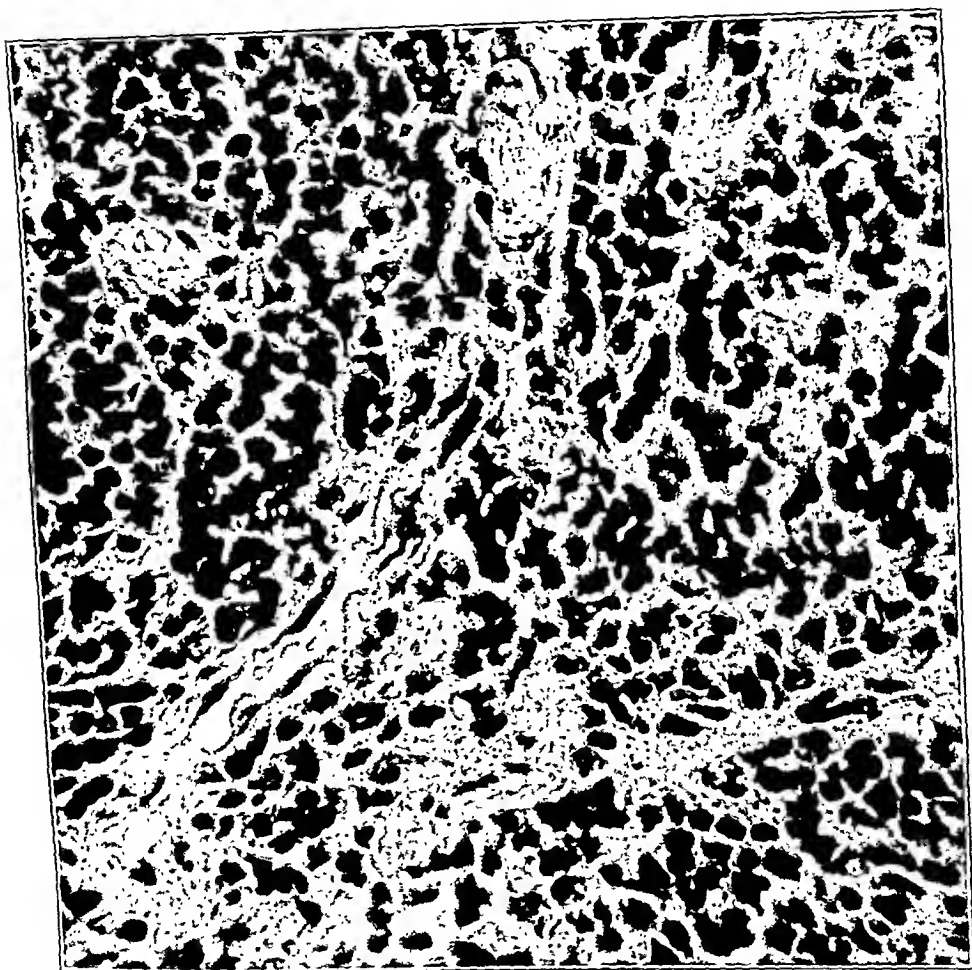


Fig. 4.—Hodgkin's disease (gastric type). Photomicrograph showing extensive granulomatous invasion of the submucosa;  $\times 250$ .

Summary: The pathologic changes noted were those of an infiltration of the distal portion of the pars media and the proximal part of the pyloric portion of the stomach. A Wassermann test was advised in order to rule out syphilis before an interpretation of the condition as a malignant process was accepted. An increased density was noted in the region of the liver. A small deposit was noted in the lower lobe of the left lung.

through this area, the wall was seen to be markedly thickened, chiefly because of an infiltration in the submucosa. The muscularis, although it was slightly hypertrophied, did not appear to be involved in the process. The mucosa of the stomach was normal in appearance except over the area already described, where definite atrophy and absence of rugae were noted. A few ridges, which appeared to be infiltrated and were definitely indurated, were seen. There was no evidence of ulceration of the mucosa.

**Microscopic Examination:** Sections which were taken from the area described showed a diffuse infiltration by round cells with dark nuclei which resembled lymphoid cells. Under a high power lens many larger cells were seen, some of which were multinucleated and resembled typical cells of Reed and Sternberg. The

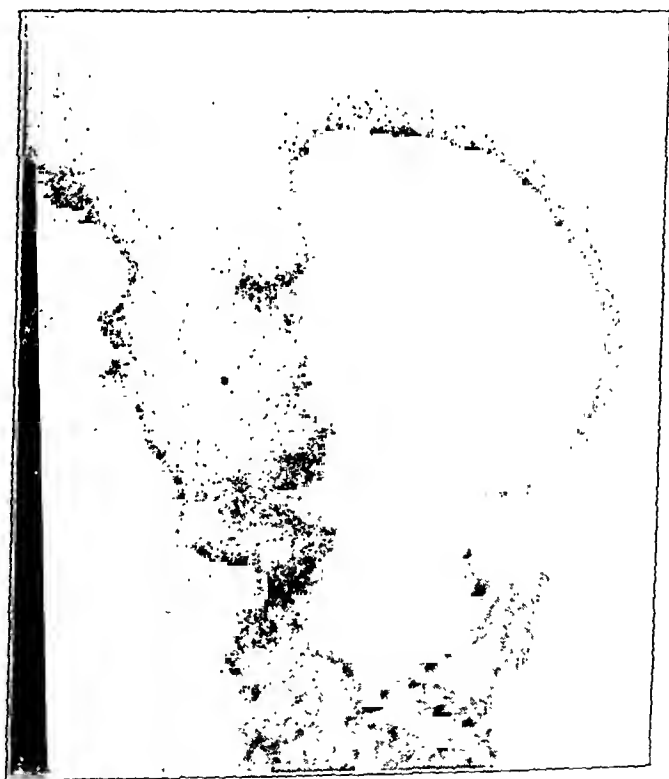


Fig. 7.—Roentgenogram made after resection of the pylorus. There is a well functioning stoma.

glands of the mucosa appeared to be normal, and there was no evidence of epithelial neoplasia. The infiltration was confined to the submucosa and mucosa and did not extend to the muscularis in any of the sections that were studied.

**Diagnosis:** ~~The diagnosis was~~ Hodgkin's lymphogranuloma.

**Postoperative Course.**—The patient left the operating room in good condition and made an uneventful recovery. On May 26 a more complete roentgenologic study was made. It showed that there was a well functioning stoma, with no residue after six hours. In the lower lobe of the left lung a small dense deposit was seen, which had the appearance of a calcified gland. The patient was discharged from the hospital on May 29 feeling perfectly well. In two months he

had gained 25 pounds (11.3 Kg.), had returned to his usual occupation, that of a helper on a farm, and was able to eat all kinds of food. A careful follow-up has shown no evidence of any recurrence and the patient continues to feel perfectly well.

#### CONCLUSIONS

1. Hodgkin's disease may originate in the lymphoid tissue of the gastro-intestinal tract and remain as a localized tumor for some time.
2. The diagnosis usually made is that of carcinoma.
3. Before the days when gastric resection was the operation of choice for gastric tumors and for infiltrating gastric ulcers, practically no cases similar to this one were reported in the literature.
4. This type of gastric lesion is a distinct clinical entity, and the favorable results which have followed operative treatment in several cases more than justify the radical operation.

## CONGENITAL ABSENCE OF PENIS

ROBERT B. DRURY, M.D.

AND

HENRY H. SCHWARZELL, M.D.

COLUMBUS, OHIO

The early literature rarely mentions congenital absence of the penis. The condition is extremely unusual. We have been able to collect only seven genuine cases in a review of the literature after 1700, although there are many examples of pseudohermaphroditism, rudimentary penis, concealment of the penis behind an abnormal duplicature of skin, hypospadia and similar abnormalities.

Saviard's report in 1702, describing "a child without a penis," is interesting:

The court surgeon at Sens wrote me during the month of January 1701, that a woman of the parish of Saint Pierre le Rond in that city had been delivered a short time previously of a child who had no penis, but instead only a small, slightly flattened eminence similar to the rump of a hen—above and alongside of which there was some fungous flesh the size of a silver crown, and a finger-width thick, round and elevated; and that the umbilicus was not in the middle of the abdomen—but above the pubes, very close to this fungous flesh.

The small eminence had two little perforations through which urine was discharged. He further stated that when the mother was questioned concerning this phenomenon, she answered that it might well be the result of the great desire she had during pregnancy to eat a chicken, because having bought one which was found to be diseased, she had been very much disappointed at not being able to satisfy her appetite.

Dufour's patient, aged 43, presented congenital tabes, complete blindness, slight nystagmus and the following congenital anomalies: a penis reduced to the size of the clitoris and surmounted by a stout cap; a fat pad resembling the labium majus on each side of the penis, double inguinal hernia, scanty development of hair, bilateral testicular atrophy, harelip, cleft palate and abnormal implantation of the teeth with the incisors in two parallel rows. Goddard's patient, born dead, had congenital absence of one leg and of the foreskin of the penis. Atkinson reported the case of a man, aged 40, who was normal with the exception of congenital absence of the glans penis. In one instance reported by Vance the corpus spongiosum was congenitally absent and was replaced by an unyielding fibrous cord. Erections resembled chordee. The left testis was atrophic, and the right one was smaller than normal. In Lemke's patient, a child 5 months of age, the penis was found beneath the scrotal skin, with the urethra emptying at the lower anterior por-

tion of the scrotum. Green, in 1879, reported the birth of a child in whom the penis was absent anteriorly as though amputated by a sharp instrument cutting forward and upward from the penoscrotal angle.

In true congenital absence of the penis the urethra has opened in or above the anus or through the perineum. Most often the urine was passed just within the anus. Complicating the discharge of urine by rectum, excoriation and ulceration developed about the anus in two of the adults. One patient anointed himself about the anus to prevent



Fig. 1.—Total absence of the penis in a boy, aged 13, of average size and weight.

irritation. Burning and itching in the rectum were troublesome in the adults and these symptoms were accompanied by chills, fever, sweats and weakness, apparently due to urinary sepsis. Though the testes were normally formed, orchitis occurred in one instance.

Two patients were infants, another was a child of 7 years and three were adults. One of the adults (Räuber, 1890) presented a small erectile eminence below the urethral opening in the anus; during sexual excitement this became swollen, and semen passed into the rectum.



Epileptic convulsions were present until the age of 30, and toxic goiter developed at the age of 38. In another adult (Göschler, 1859) there was an erectile mass on the perineum in front of the anus. Excitement

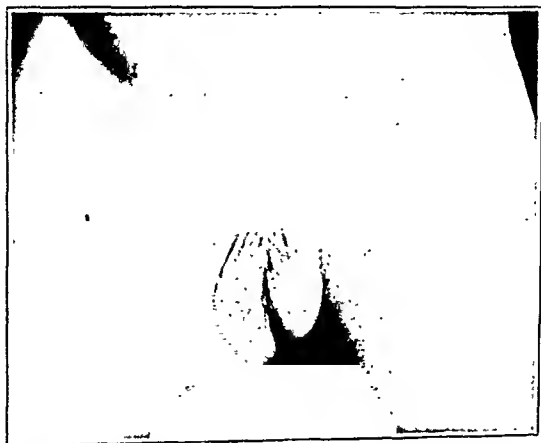


Fig. 2.—Normally formed scrotum and testis. There was no hernia or hydrocele. The raphe was present anteriorly.

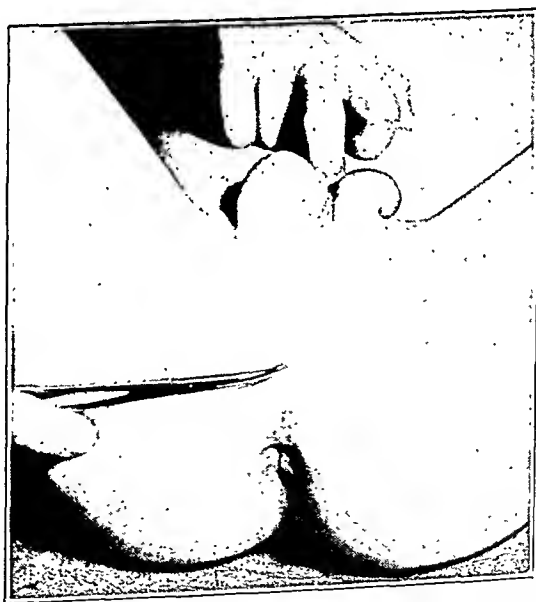


Fig. 3.—Normal perineum and anus. The anterior end of the raphe is indicated by the forceps.

produced by friction over this tissue induced orgasm and a discharge of semen into the anus. Death occurred in one instance at the age of 30. This was due to infection of the kidney following a simple operation for hemorrhoids; the man had been married several years.

It will be noticed that in even the seven collected cases of true congenital absence of the penis, additional anomalies complicated the picture



Fig. 4.—Absence of the raphe from the posterior aspect of the scrotum.

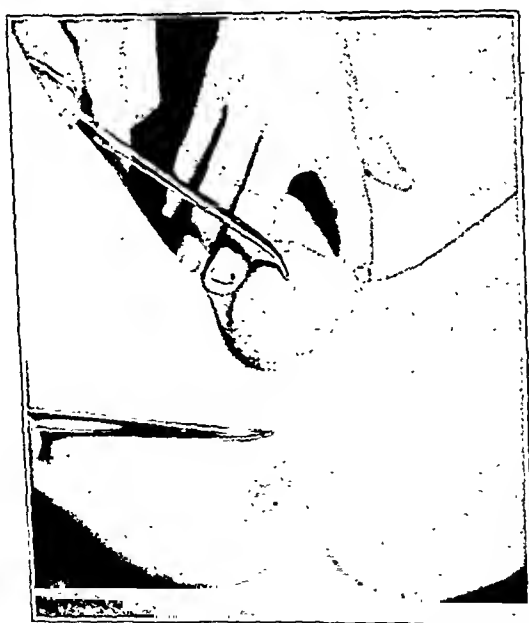


Fig. 5.—The upper forceps points to a cicatricial mark at the end of the scrotal raphe. The raphe is absent between the points indicated by the forceps.

often. Thus, erectile tissue occurred on the perineum in one patient and inside the anus in another; epilepsy was present in one adult, and Nealon's patient (1854), an infant, had hydrocele on the left side.

The following case is one of true congenital absence of the penis, remarkable because of the absence of symptoms and the lack of accompanying anomalies.

#### REPORT OF A CASE

W. C., a 13 year old white boy, was referred to us by Dr. Moccabee of Cardington, Ohio, in January 1931. His parents stated that he had been born without a penis. There was otherwise nothing significant in the history. The child had been healthy, had played as other children of his age and had never presented symptoms



Fig. 6.—Roentgenogram taken sixty minutes after injection of dye intravenously. The bladder is outlined in front of the sacral promontory. The ureters are visualized. The dye has entered the rectum below the bladder.

suggestive of urinary infection. Urine was voided through the rectum, but the child was unable to distinguish the desire to defecate from the call to pass urine. The parents observed that, though this boy had three or four bowel movements a day, the stools were often liquid and quite clear.

On physical examination the boy appeared healthy and normal except for total absence of the penis. His physical and mental development and his manner were about the same as those of the average boy of his age. The changes of puberty had not yet occurred. Close examination of the scrotum and perineum revealed

not the slightest trace of a vestigial penis or other rudimentary structure suggesting a penis. The scrotum was normally formed, and contained two normal, fully descended testes, and the spermatic funiculus and vas were palpable as usual on each side. There was no hydrocele or hernia. The right testis was placed somewhat lower in the scrotum than the left. The raphe was absent from the posterior aspect of the scrotum and extended only 1 inch (2.5 cm.) anteriorly from the anus onto the perineum. The raphe on the anterior scrotal wall terminated in a small cicatricial mark at the dependent portion of the sac. The anus was entirely normal, and there were no ulcers or excoriations in this region.

Proctoscopic examination revealed no trace of a urinary orifice near the anus, but urine was seen to trickle along the anterior wall of the rectum. The opening



Fig. 7.—Roentgenogram taken thirty minutes following the injection of iopax. The fusiform sacculuation of each ureter is seen opposite the fifth lumbar vertebra.

was apparently small and hidden in an anterior fold of rectal mucosa. Urography after intravenous injection of iopax disclosed the presence of bilateral hydro-ureter, most marked opposite the fifth lumbar vertebra. Each ureter presented a sacculuation at this level. The pelves of the kidney were fairly visible and moderately dilated. The bladder outlined by the dye lay opposite the sacro-iliac joints and extended upward to the middle of the fifth lumbar vertebra. No urethra could be visualized. We advised against ureteral catheterization and cystoscopy because of the likelihood of producing urinary infection.

#### SUMMARY

True congenital absence of the penis is extremely rare. In the seven cases previously recorded accompanying congenital defects were common,

and ectopic erectile tissue was often noted. It is probable also that hydro-ureter and hydronephrosis would have been frequently observed in these instances had the present methods of urologic investigation been available. So far as we can determine, this is the first time such a patient has been studied by urography following intravenous injection. The case is particularly unusual because examination revealed no other external abnormalities.

## BIBLIOGRAPHY

- Aimes, A.: Absence apparente de la verge, malformation de la muqueuse préputiale, *Rev. d'ortop.* **6**:567, 1918.
- Atkinson, I. E.: Congenital Absence of the Glans Penis, *New York M. J.* **68**: 668, 1898.
- Collier, J.: Malformation of External Genitals in the Male, *Brit. M. J.* **1**:409, 1889.
- Dufour, H. W., and Casteran, R.: Tardy Congenital Tabes in Subject with Congenital Syphilis, Presenting Numerous Deformities, *Bull. et mém. Soc. méd. d. hôp. de Paris* **1**:1104, 1926.
- Fáykiss, F.: Defectus penis et scroti, *Budapesti k. m. t. egyet. 2. sz. Seb. Klin. betegf.* 1903-1904, Budapest, 1905, p. 70.
- Fröhlich, C. L.: Affections of the Penis, *South African M. J.* **4**:593 (Oct. 11) 1930.
- Ginteras, R.: Urology, New York, D. Appleton and Company, 1912, vol. 2, p. 518.
- Goddard, H. S.: Unusual Case of Abnormality of the Penis, *M. J. & Rec.* **133**: 87, 1931.
- Göschler: Mangelhafte Bildung der äusseren Genitalien, *Vrtljschr. f. d. prakt. Heilk.* **53**:98, 1859.
- Green, W. E.: Congenital Absence of the Penis, *Homœop. J. Obst.* **1**:423, 1879-1880.
- Harris, R. P.: Congenital Absence of the Penis, the Urethra Making Its Exit Into or Below the Rectum, and Emptying into the Bladder by, or Exterior to, the Anus, *Philadelphia M. J.* **1**:71, 1898.
- Lemke, F.: Angeborener Mangel des Penis, *Virchows Arch. f. path. Anat.* **133**: 181, 1893.
- Mathews, J. M.: Urethra Opening into Rectum, Patient Born Without a Penis, *Am. Practitioner & News* **17**:27, 1894.
- Néalton: Absence de penis chez un enfant nouveau-né, *Gaz. d. hôp.* **27**:45, 1854.
- Räuber: Angeborener Mangel des männlichen Gliedes, *Virchows Arch. f. path. Anat.* **121**:604, 1890.
- Reverdin, A.: Absence congénitale presque complète des organes génitaux chez un homme de 31 ans, *Bull. et mém. Soc. d. chirurgiens de Paris* **31**:70, 1905.
- Revolat: *J. gén. de méd., de chir. et de pharm.* **27**:370, 1806.
- Saviard: Nouveau recueil d'observations chirurgicales, Paris, Jacques Collombat, 1702, p. 518, Case 118.
- Vance, A. M.: Congenital Defect of the Penis, *Pediatrics* **13**:213, 1902.

# EFFECTS OF LOCAL IMMUNIZATION ON THE DEVELOPMENT OF EXPERIMENTAL ABSCESSSES OF THE LUNG

WILLIAM M. TUTTLE, M.D.

ST. LOUIS

AND

PAUL R. CANNON, M.D.

CHICAGO

The development of experimental methods for the production of abscesses in the lungs of dogs has contributed materially to the knowledge of the pathogenesis, complications and treatment of similar infections in man, but information as to means of prevention is still rather meager. This study deals with the preventive phase of the problem and presents data which justify the hope that localized infections of this sort can to some extent be prevented, or at least that their ill effects can be lessened.

An adequate understanding of the ways by which the lungs prevent or resist the progress of infectious agents within them depends on a proper recognition of their structural and functional characteristics under both normal and abnormal conditions. The remarkable extent to which the lungs of the average city dweller filter out and retain coal dust and the infrequency with which such particles are disseminated through the blood stream indicate the presence of an unusually efficient barrier to the hematogenous distribution of particulate exogenous agents. As the progress of inhaled materials must end in the smallest units of pulmonary structure, the alveoli, the principal barrier is evidently the alveolar wall. This wall consists of reticulum, collagen and capillary endothelium and is lined by or contains within it the alveolar macrophages or septal cells. Although the origin of these cells is uncertain, pathologic and experimental evidence reveals that they have definite phagocytic proclivities while they are attached to the septum or while they are free in the alveolar spaces. Particles entering the alveolar spaces must therefore necessarily come in contact with many of these cells, and the numbers and phagocytic potentialities of the latter will determine, to a large extent, the fate of the particles. Experimental evidence supports this view. For example, foreign corpuscles

---

From the Department of Pathology, the University of Chicago. This work was done under a grant from the Douglas Smith Foundation for Medical Research of the University of Chicago.

(Briscoe<sup>1</sup>), bacteria (Fried<sup>2</sup>) and such materials as india ink, trypan blue and carmine (Sewell,<sup>3</sup> Foot,<sup>4</sup> Gardner and Smith,<sup>5</sup> Lang<sup>6</sup> and Fried<sup>7</sup>) when injected intratracheally are engulfed primarily by the pulmonary macrophages, and comparatively small amounts directly enter the blood stream.

A similar barrier effect presumably occurs when living bacteria are inhaled, and the well known primary complex in tuberculosis illustrates the ability of the lungs to localize the tubercle bacilli of the first infection. The earliest stage of the localizing mechanism probably consists in the adherence of the bacteria to the wall of the alveolar septum or their early engulfment by macrophages or leukocytes within the lungs. Although the ultimate fate of the micro-organisms depends on their ability to grow within the affected tissues or cells, the essential initial conflict is between the invading bacteria and the pulmonary phagocytes.

This early local phagocytic reaction suggests that conditions of local immunity may modify the extent of exogenous pulmonary infection. Several investigators, indeed, have obtained evidence for the existence of a local pulmonary immunity. For example, animals immunized intratracheally with killed diphtheria bacilli have acquired a resistance to many lethal doses of the homologous living organism subsequently introduced intratracheally, although animals used as controls, which were subcutaneously immunized, died after similar intratracheal injections. Conversely, animals immunized intratracheally were not protected against intravenous injections of live diphtheria bacilli (Besredka<sup>8</sup>). Pfenninger<sup>9</sup> demonstrated that rabbits may be ten times as resistant to the intratracheal injection of living paratyphoid bacilli

---

1. Briscoe, J. C.: An Experimental Investigation of the Phagocytic Action of the Alveolar Cells of the Lungs, *J. Path. & Bact.* **12**:66 (Jan.) 1908.

2. Fried, B. M.: The Infection of Rabbits with the Anthrax Bacilli by Way of the Trachea, *Arch. Path.* **10**:213 (Aug.) 1930.

3. Sewell, W. T.: Phagocytic Properties of the Alveolar Cells of the Lungs, *J. Path. & Bact.* **22**:40, 1918.

4. Foot, N. C.: Studies on Endothelial Reactions: Origin of the Pulmonary "Dust Cells," *Am. J. Path.* **3**:413 (Sept.) 1927.

5. Gardner, L. U., and Smith, D. T.: Origin of the Alveolar Phagocyte Studied in Paraffin Sections of Tissues Stained Supravitaly with Neutral Red, *Am. J. Path.* **3**:445 (Sept.) 1927.

6. Lang, F. J.: Ueber Gewebeskulturen der Lunge. Ein Beitrag zur Histologie des respiratorischen Epithels und zur Histogenese der Alveolarphagocyten, *Arch. f. exper. Zellforsch.*, **2**:93, 1926.

7. Fried, B. M.: Defensive and Metabolic Apparatus of the Lungs; Lungs and the Macrophage System, *Arch. Path.* **6**:1008 (Dec.) 1928; The Origin of the Histiocytes (Macrophages) in the Lungs, *ibid.* **3**:751 (Nov.) 1927.

8. Besredka, A.: Infection and Vaccination by the Trachea, *Ann. Inst. Pasteur* **34**:361 (May) 1920; The Actions of Serums on the Respiratory Tract, *ibid.* **34**:51 (Jan.) 1920.

9. Pfenninger, L.: The Importance of the Respiratory Tract in the Production of Antibodies, *Ann. Inst. Pasteur* **35**:237 (April) 1921.

as to the intravenous injection of approximately equal numbers of the same organism. Cecil and Steffen<sup>10</sup> obtained complete immunity to pneumococcic pneumonia in monkeys immunized intratracheally with a pneumococcus vaccine, although the blood serum failed to protect mice against the intraperitoneal injection of small quantities of the culture. Similarly, Jones<sup>11</sup> showed that intratracheal immunization of rabbits with a killed culture of *Bacillus avisepticus* protected them against intratracheal injection of amounts of living culture invariably fatal for normal rabbits. An increased pulmonary resistance to pneumococci introduced into the lungs of rabbits rendered immune by the previous intratracheal administration of a heat-killed vaccine of the homologous organism has been observed by Stuppy, Cannon and Falk.<sup>12</sup> More recently Burt, Tuttle and Cannon<sup>13</sup> have demonstrated that the efficiency of the pulmonary barrier can be markedly enhanced by intratracheal immunization, as shown by the decreased tendency to invasion of the blood stream when virulent pneumococci are introduced intratracheally. Coggeshall and Robertson<sup>14</sup> have shown that experimental lobar pneumonia produced in dogs which have recently recovered from pneumonia is characterized by resistance to a significantly larger infecting dose than the normal animal can withstand and by a decreased tendency to invasion of the blood stream. These experiments suggest that the pulmonary tissues, when stimulated by local contact with antigen, acquire a greater ability to resist and overcome subsequent infections. This does not imply, however, that general agencies do not also participate in the process. The following experiments were performed in an attempt to secure additional information as to the effects of local pulmonary immunization on the course and development of experimental pulmonary abscesses in the dog.

#### METHODS

Dogs weighing from 12 to 15 Kg. were used. All of the animals were isolated in clean kennels for from seven to ten days, and those in which signs of distemper developed were discarded.

---

10. Cecil, R. L., and Steffen, G. I.: Vaccination of Monkeys Against Pneumococcus Type I Pneumonia by Means of Intratracheal Injection of Pneumococcus Type I Vaccine, *Pub. Health Rep.* **37**:2735 (Nov. 3) 1922.

11. Jones, F. S.: The Influence of Resistance on the Character of the Disease in Experimental Respiratory Infection, *J. Exper. Med.* **39**:725, 1924.

12. Stuppy, G. W.; Cannon, P. R., and Falk, I. S.: Nature of Immunity in the Lungs of Rabbits Following Immunization with Pneumococci, *J. Prev. Med.* **5**:97 (March) 1931.

13. Burt, K. L.; Tuttle, W. M., and Cannon, P. R.: Studies in Local Immunization of the Lungs of Rabbits to Type I Pneumococcus, *Proc. Soc. Exper. Biol. & Med.* **30**:1138 (May) 1933.

14. Coggeshall, L. T., and Robertson, O. H.: Observations on Repeated Attacks of Experimental Pneumococcic Lobar Pneumonia in Dogs, *Arch. Path.* **16**:306 (Aug.) 1933.



Ninety-seven dogs were used, twenty-two of which were for such preliminary work as the determination of the proper time of rest between vaccination and embolization and the optional number of vaccinations. This paper describes the results obtained in seventy-five dogs, divided into four series as follows:

	Number of Animals
Series 1 Intratracheally immunized (specific).....	33
Series 2 Intratracheally immunized (nonspecific).....	4
Series 3 Subcutaneously immunized (specific).....	5
Series 4 Normal control animals.....	33

Vaccines of *Staphylococcus aureus* and *Bacillus coli* were prepared as follows: Kille flasks containing blood agar were inoculated and incubated at 37 C. for twenty-four hours, after which the growth was suspended in a sterile 0.85 per cent solution of sodium chloride containing 0.3 per cent by volume of a 37 per cent solution of formaldehyde. This type of vaccine was used because of the probability of less denaturization of the antigen complex. The vaccine was kept in the icebox for from three to four days or until it was sterile; it was then centrifugated, and the sediment was resuspended in twice the amount of sterile 0.85 per cent solution of sodium chloride.

In these experiments two bacterial strains were used: (1) a culture of *Staph. aureus* isolated from the clavicle of a boy suffering from multiple foci of osteomyelitis; (2) a culture of *B. coli* isolated from the kidney of a man acutely ill with pyonephrosis. Proper virulence of both cultures was secured by serial inoculations into the abdominal wall of dogs until abscesses were regularly produced at the site of injection. The virulence of the bacteria was sustained by recovering the micro-organisms from the pulmonary abscesses produced in the course of the experiments.

The dogs were narcotized with morphine sulphate (2 grains [0.13 Gm.]) and atropine sulphate ( $\frac{1}{15}$  grain [0.0009 Gm.]) in order to render them quiet for the introduction of the bronchoscope.

The vaccine was sprayed into the main bronchi by means of a special spray tube introduced through the bronchoscope. In some of the animals studied early, as will be noted in table I, the vaccine was diluted, and from 10 to 20 cc. was introduced into each main bronchus through a long metal tube. In order to avoid the introduction of such large amounts of fluid, the spray method was used in the animals studied later. As a rule, two vaccinations were sufficient to establish a definitely increased resistance, but in the earlier series four inoculations were given at intervals of from three to four days.

The method of Holman, Cutler, Weidlein and Schlueter,<sup>15</sup> for the experimental production of pulmonary abscesses had certain disadvantages in this study: The emboli did not contain the same number of organisms; the wall of the vein was not absorbed after weeks or even months, and the lead shots, as well as the

15. Holman, E.; Weidlein, I. F., and Schlueter, S. A.: A Method for the Production of Lung Abscesses, *Proc. Soc. Exper. Biol. & Med.* **23**:266 (Jan.) 1926. Cutler, F. C., and Schlueter, S. A.: Experimental Production of Abscesses of the Lung, *Ann. Surg.* **84**:256 (Aug.) 1926. Weidlein, I. F., and Schlueter, S. A.: Postoperative Lung Abscesses: An Experimental Study, *Arch. Surg.* **14**:457 (Feb.) 1927. Cutler, E. C.; Schlueter, S. A., and Weidlein, I. F.: Experimental Production of Lung Abscesses, *New York State J. Med.* **26**:767 (Sept. 15) 1926.

threads used to tie the ends, constituted foreign bodies in the tissues. Furthermore, owing to these foreign bodies, it was impossible to make microscopic sections of an abscess with the embolus in situ.

In a previous paper, one of us<sup>16</sup> described the use of an agar embolus for the production of pulmonary abscesses. This method seemed better suited to the present experiments and was used throughout.

The agar emboli, which contained living bacteria, were introduced into the external jugular vein as follows: The animal was narcotized, and the skin of the left side of the neck was shaved, cleansed and painted with iodine. The skin and the subcutaneous tissue of the neck were infiltrated with 2 per cent

TABLE 1.—*Comparison of the Size of the Abscess Cavity in Normal Dogs and in Locally Immunized Dogs Ten Days After Embolization*

No.	Micro-Organism in Vaccine	Route of Immunization	Micro-Organism in Embolus	Size of Abscess Cavity, Cm.*	Amount of Vaccine, Cc.	Number of Vaccinations	Time of Rest Period, Days
1	Normal	.....	Staph. aureus	0.9	..	..	..
2	Normal	.....	Staph. aureus	1	..	..	..
3	Normal	.....	B. coli	0.8	..	..	..
4	Normal	.....	B. coli	1 by 0.5	..	..	..
5	Normal	.....	B. coli	0.5	..	..	..
6	Normal	.....	B. coli	1 by 0.5	..	..	..
7	Normal	.....	B. coli	1	..	..	..
8	Normal	.....	B. coli	0.7 by 0.5	..	..	..
9	Normal	.....	B. coli	2 by 3	..	..	..
10	Normal	.....	B. coli	0.5	..	..	..
11	Normal	.....	Staph. aureus	0.8 by 0.4	..	..	..
12	Normal	.....	Staph. aureus	0.8	..	..	..
13	Normal	.....	B. coli	0.5	..	..	..
14	Normal	.....	B. coli	0.5	..	..	..
15	Staph. aureus	Intratracheal	Staph. aureus	0.5 by 0.3	40	8	41
16	Staph. aureus	Intratracheal	Staph. aureus	0	40	3	41
17	Staph. aureus	Intratracheal	Staph. aureus	0	40	3	41
18	Staph. aureus	Intratracheal	Staph. aureus	0	40	3	41
19	B. coli	Intratracheal	B. coli	0.2	20	4	23
20	B. coli	Intratracheal	B. coli	0	20	4	23
21	B. coli	Intratracheal	B. coli	0	20	4	23
22	B. coli	Intratracheal	B. coli	0.8	20	4	23
23	B. coli	Intratracheal	B. coli	0	10	2	29
24	B. coli	Intratracheal	B. coli	0	10	2	29
25	B. coli	Intratracheal	B. coli	0	10	2	29
26	B. coli	Intratracheal	B. coli	0	10	2	29
27	B. coli	Intratracheal	B. coli	0.1	10	2	29
28	B. coli	Intratracheal	B. coli	0	10	2	29

\* The size of the abscess cavity was determined by measuring from one edge of the cavity to the other; if the abscess was round or almost round, only one dimension appears; if the cavity was oval, two dimensions are given.

0 is the symbol adopted to imply that no cavity existed, and that the embolus was touched on all sides by the surrounding inflammatory tissue, as shown in figure 4.

procaine hydrochloride, a small incision was made, and the external jugular vein was freed from the subcutaneous fat. The vein was incised, and the embolus introduced and washed down with an 0.85 per cent solution of sodium chloride, after which the vein was tied above and below the incision and the skin closed.

The animal was killed by electrocution, and the lungs were removed with the trachea clamped. The tissues were fixed in Zenker's solution which did not contain acetic acid and to which a diluted solution of formaldehyde, U. S. P. (1:10), made neutral, had been added: they were next embedded in celloidin,

16. Tuttle, W. M.: A New Method for the Production of Experimental Abscesses of the Lungs in Dogs, *Proc. Soc. Exper. Biol. & Med.* 30:462 (Jan.) 1933

and sections were cut at from 10 to 12 microns and stained with Maximow's eosin azure and Mallory's triple connective tissue stain.

In the triple stain the celloidin sections, after removal of the celloidin, were stained for twelve hours in a dilute solution of Delafield's hematoxylin and were then stained overnight in a mixture of 10 cc. of 1 per cent water-soluble eosin (Gibbs), diluted in 100 cc. with distilled water, and 10 cc. of a 1 per cent aqueous solution of azure 2. The connective tissue stain was Mallory's aniline blue and picrocarmagel combination, prepared according to the formula given by Mallory and Wright<sup>16a</sup>.

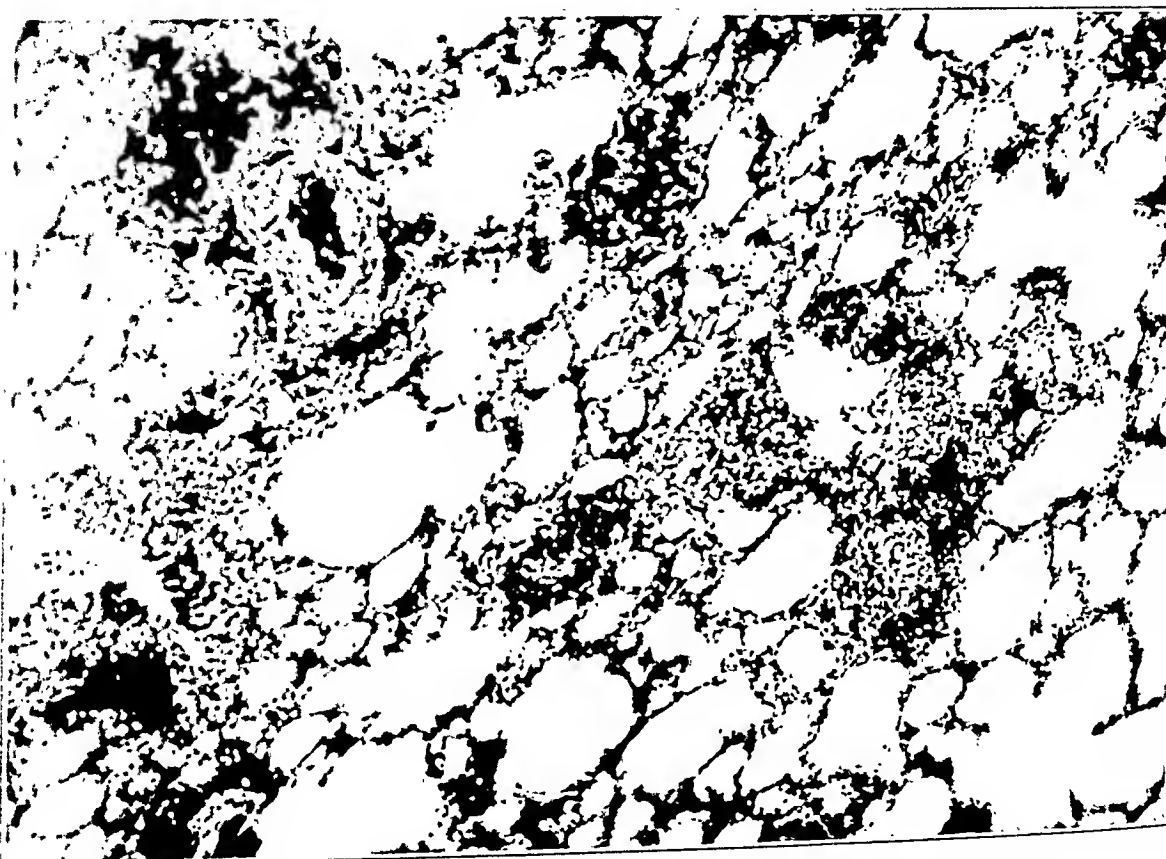


Fig. 1.—Photomicrograph of a section from the lung of a dog vaccinated intratracheally with a vaccine of *B. coli* killed by formaldehyde. Note the accumulations of basophilic mononuclear cells around the blood vessels;  $\times 88$ .

#### EFFECTS OF AN INTRATRACHEAL INJECTION OF A VACCINE CONTAINING FORMALDEHYDE ON THE LUNGS OF NORMAL ANIMALS

In order to determine the changes which may occur in normal lungs following the intratracheal administration of antigen, dogs were immunized by having their lungs sprayed with 6 cc. of a vaccine of *B. coli* killed with formaldehyde—3 cc. into each main bronchus. One week

16a. Mallory, F. B., and Wright, J. H.: *Pathologic Technique*, Philadelphia, W. B. Saunders Company, 1924.

later the lungs were sprayed with 4 cc. Eighteen days after this the animals were killed, and the lungs examined grossly and microscopically.

On macroscopic examination the lungs appeared normal. Microscopic examination showed an essentially normal picture except for a slight thickening of the alveolar walls and the presence in the perivascular and peribronchial tissues of a "collar" of basophilic mononuclear cells. This so-called "mantling" (fig. 1) occurred in the lungs of all three animals; it was most marked about the arteries and bronchi but present also about the smaller blood vessels. The cells were large mononuclear cells with deeply staining nuclei. Mitotic figures were seen frequently, and the cells appeared to be multiplying rapidly in situ.

The exact significance of the reaction is uncertain, but presumably it indicates a mesenchymal activation and mobilization of potentially phagocytic cells derived from a local proliferation or a hematogenous emigration of mononuclear cells. It furnishes, however, a morphologic basis for the assumption that increased numbers of these cells may aid in elevating the resistance of the lungs both through their maturation into phagocytes and through their presumed ability to participate in the formation of antibodies.

#### A COMPARISON OF THE REACTIONS OF NORMAL AND IMMUNE LUNGS TO THE INTRODUCTION OF AN EMBOLUS INFECTED WITH THE HOMOLOGOUS ORGANISM

Fourteen healthy dogs were immunized as described earlier—four with a *Staph. aureus* vaccine, and ten with a vaccine prepared from *B. coli*. Four of the animals (dogs 15, 16, 17 and 18) were immunized at intervals of from three to four days by the introduction through a long metal tube on three occasions of 20, 10 and 10 cc., respectively, of the original vaccine diluted 1:10 with a sterile 0.85 per cent solution of sodium chloride. The remaining ten animals received smaller amounts of the original *B. coli* vaccine introduced into the lungs by means of the spray apparatus. Four vaccinations with 5 cc. each were given dogs 19, 20, 21 and 22, and two vaccinations with 6 and 4 cc., respectively, were given to the remaining six dogs (23 to 28, inclusive). From twenty-three to forty-one days after the last immunization, an embolus infected with the homologous organism was introduced into the external jugular vein. The animals were observed for ten days, after which they were killed and the lungs examined. Fourteen normal dogs were embolized simultaneously with similar emboli and were killed ten days later. The summarized details for this group are given in table 1. The following protocols for a normal control animal and one intratracheally immunized illustrate the typical observations.

DOG 2.—A normal animal was narcotized with morphine sulphate (2 grains) on Oct. 6, 1932, and an embolus infected with *Staph. aureus* was introduced

into the external jugular vein. On October 7 the animal appeared to be normal; it remained normal until the tenth day, when it was killed by electrocution.

*Necropsy.*—Autopsy was performed on October 17. The pleural surfaces were smooth and glistening. There were no adhesions or fluid in the pleural cavities. The lungs contained air and were grossly normal except for the presence at the inner margin of the left lower lobe of a mass measuring 3 by 5 cm. When sectioned, the area consisted of a deeply hemorrhagic pulmonary parenchyma containing an abscess cavity 1 cm. in diameter and filled with a thick, yellow pus in which the agar embolus was lying free. The wall was composed of necrotic material, and no definite pyogenic membrane surrounded the abscess cavity.

*Microscopic Examination.*—Sections taken through the abscess showed that the embolus was missing from the cavity, which was surrounded by a broad zone of polymorphonuclear leukocytes, many of which contained engulfed bacteria, although the number of micro-organisms per leukocyte was few. On one side were many new blood vessels and young fibroblasts. Farther from the cavity were numerous large macrophages containing polymorphonuclear leukocytes and occasional bacteria. There was only a slight fibroblastic reaction at the edge of the leukocytic zone, and the contiguous pulmonary tissue showed little evidence of mesenchymal mobilization.

TABLE 2.—Comparison of the Size of the Abscess Cavity in Normal, Locally Immunized and Generally Immunized Animals Ten Days After Embolization\*

No.	Micro-Organism in Vaccine	Route of Immunization	Micro-Organism in Embolus	Size of Abscess Cavity, Cm.	Amount of Vaccine, Cc.†	Number of Vaccinations	Time of Rest Period, Days
15	Staph. aureus	Intratracheal	Staph. aureus	0.5 by 0.3	40	3	41
16	Staph. aureus	Intratracheal	Staph. aureus	0	40	3	41
17	Staph. aureus	Intratracheal	Staph. aureus	0	40	3	41
18	Staph. aureus	Intratracheal	Staph. aureus	0	40	3	41
1	Normal	.....	Staph. aureus	0.9	..	..	..
2	Normal	.....	Staph. aureus	1	..	..	..
29	Staph. aureus	Subcutaneous	Staph. aureus	0.2	24	3	41
30	Staph. aureus	Subcutaneous	Staph. aureus	0.8	24	3	41
31	Staph. aureus	Subcutaneous	Staph. aureus	0.6 by 0.3	24	3	41
32	B. coli	Subcutaneous	B. coli	0.3	10	2	45
33	B. coli	Subcutaneous	B. coli	0.7	10	2	45

\* The size of the abscess cavity was determined in the manner indicated in table 1.

† The vaccine given subcutaneously to dogs 29, 30 and 31 was a 50 per cent solution of the original vaccine, whereas that given intratracheally to dogs 15, 16 and 18 was a 10 per cent solution of the original vaccine. The vaccine given dogs 32 and 33 was a 50 per cent solution of the original vaccine.

Dog 17.—An immune dog was narcotized with morphine sulphate (2 grains) and atropine sulphate ( $\frac{1}{15}$  grain) on Aug. 18, 1932. Twenty cubic centimeters of a suspension of Staph. aureus killed with formaldehyde was instilled into the lung through a long metal tube—10 cc. into each main bronchus.

Five days later a similar dose of 10 cc. was introduced, and after three days another dose of 10 cc. was given. Throughout the next five weeks the animal remained well.

On October 6 an agar embolus infected with Staph. aureus was introduced into the left external jugular vein; the animal was killed ten days later.

*Necropsy.*—There was a dark red mass in the lower lobe of the left lung. The overlying pleura appeared to be normal. This mass, when sectioned, consisted of a consolidated area 1.7 cm. in diameter, the outer part of which was a deep red. The inner portion was light, yellowish gray and contained in its center the agar embolus tightly surrounded by inflammatory tissue. No definite cavity caused by an abscess was present.

*Microscopic Examination.*—The embolus was in place, and at its outer borders the bacterial colonies appeared as dark blue masses, whereas at the center of the embolus the colonies had degenerated and were pale pink. The embolus was immediately surrounded by a narrow zone of polymorphonuclear leukocytes, red blood cells and macrophages. This thin zone was sharply circumscribed by fibroblasts, a few polymorphonuclear leukocytes and many darkly staining mononuclear cells. There were comparatively few bacteria outside the embolus, although small numbers were occasionally seen within the polymorphonuclear leukocytes and macrophages. The blood vessels contained numerous monocytes, and macrophages with a foamy cytoplasm and containing remnants of leukocytes were seen in the



Fig. 2.—Photomicrograph of an abscess present in a normal dog (2) ten days after the introduction into the external jugular vein of an embolus infected with *Staph. aureus*. Note the large, irregular cavity formed by the abscess and the extensive inflammatory reaction in the surrounding pulmonary tissues;  $\times 7$ .

contiguous tissues. The area of inflammatory infiltration was sharply circumscribed, and the bacteria were not disseminating.

In general the observations on the lungs of the normal animals were similar to those previously obtained and described by other investigators. An abscess varying from 0.5 to 3 cm. in diameter always formed in the normal animals. The walls of the abscess cavities were ragged, and there was little evidence of healing. Hemorrhagic infarction distal to the abscess occurred frequently. In one animal (dog 9) a large abscess

with a necrotic wall and accompanying massive infarction of the entire lobe had led to perforation, purulent pleuritis and death on the ninth day after embolization.

The microscopic picture (figs. 2 and 3) indicated an advancing rather than a controlled infection. The abscess cavity was surrounded by a leukocytic wall varying from 1 to several millimeters in thickness through which bacteria, both intracellular and extracellular, were scattered. Fibroblasts were numerous only in the abscesses which developed

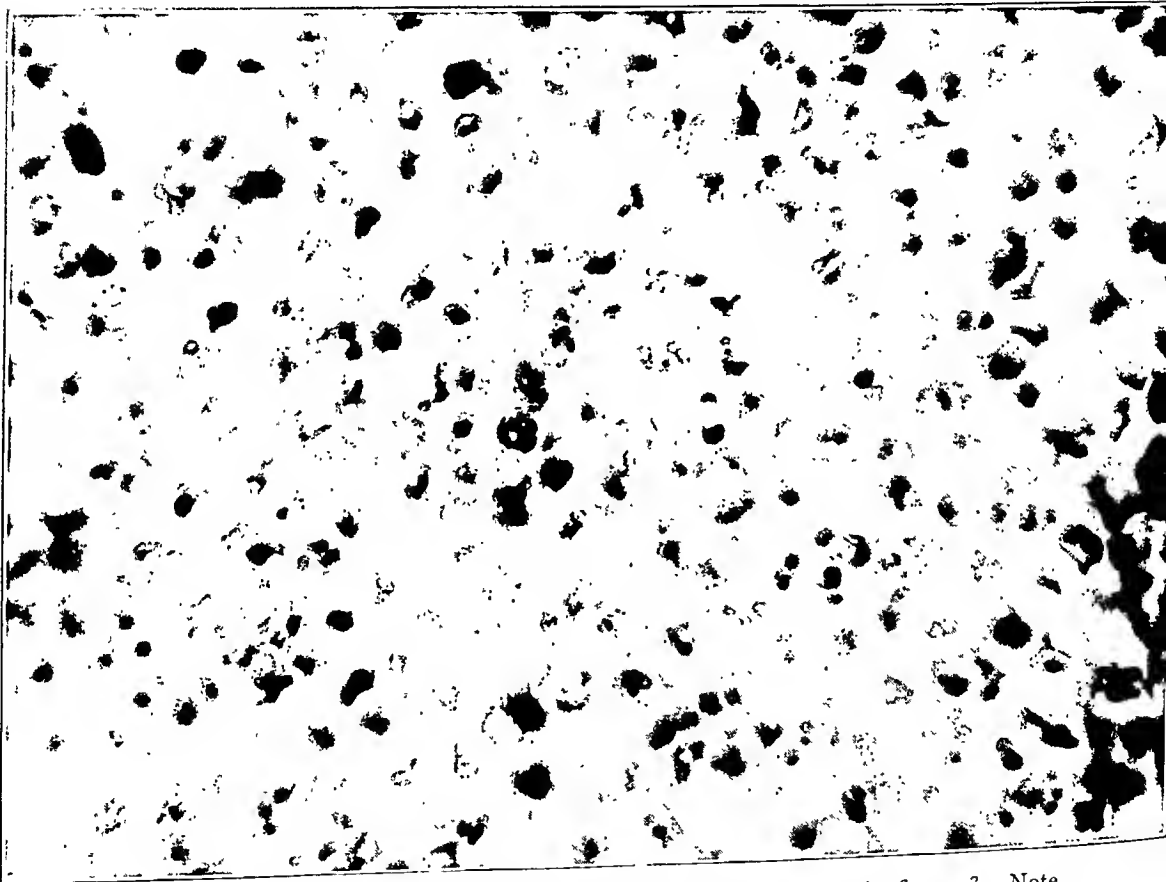


Fig. 3.—Photomicrograph of the wall of the abscess shown in figure 3. Note the predominance of polymorphonuclear leukocytes and the absence of fibroblasts;  $\times 815$ .

near the larger blood vessels and the bronchi and which appeared to be streaming in from the walls of these structures rather than arising from the mononuclear phagocytes. The mantling reaction was seen occasionally, but not to the extent observed in the immunized animals.

The reactions in the lungs of the immune dogs contrasted sharply with those observed in the normal animals. In only four of the fourteen immune animals did cavitation occur (dogs 15, 19, 22 and 27), and in two of these (dogs 19 and 27) the abscess cavity was small. A large abscess formed in dog 22. As it has been shown that chronic

cough tends to increase greatly the size and chronicity of abscesses in the dog (Van Allen, Cole and Fox<sup>17</sup>), it is of interest that dog 22 coughed considerably before and after embolization.

The embolus in the immune animals was surrounded by a rather dense zone, varying from 2 to 10 mm. in width, of whitish-gray exudate. The average diameter of the abscess cavity in the four of the fourteen immune animals in which cavitation occurred was approximately 0.4

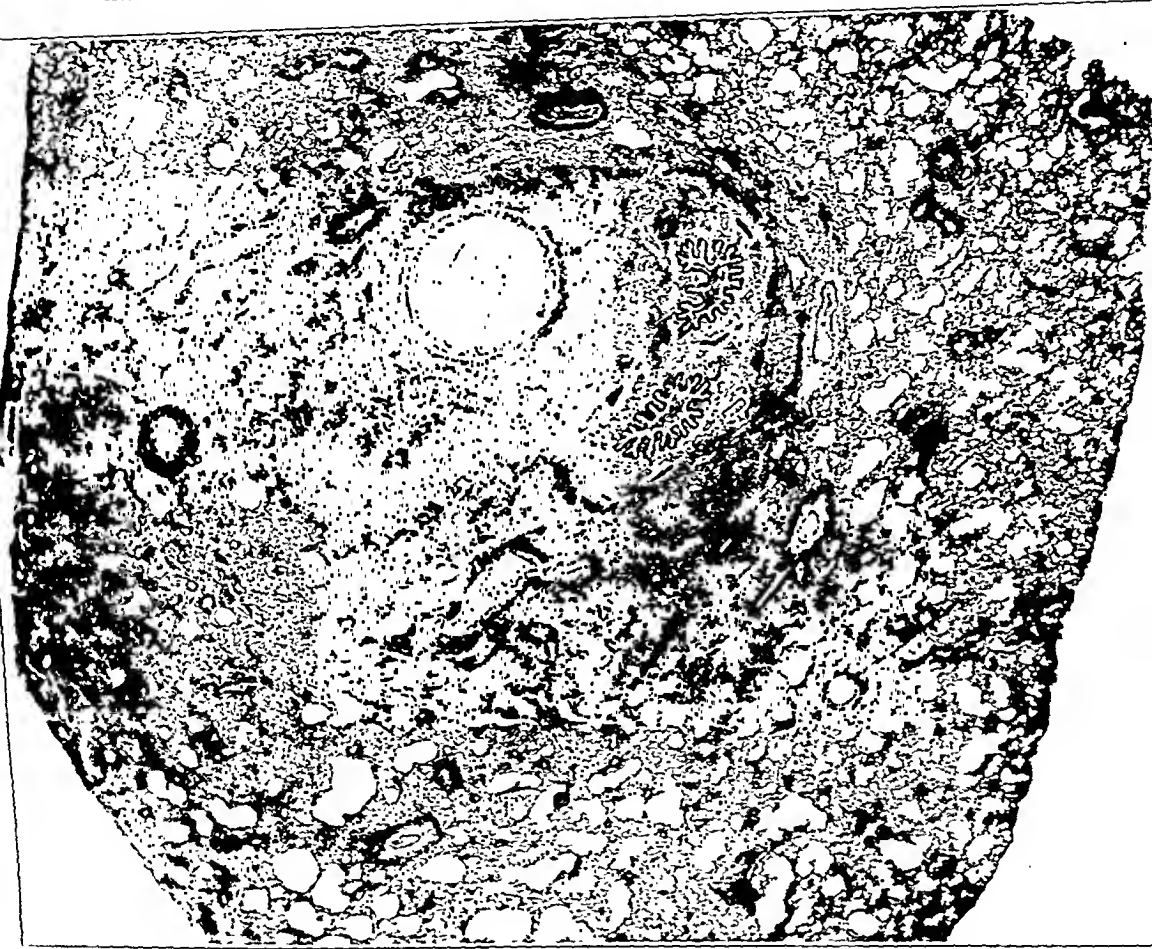


Fig. 4.—Photomicrograph of the abscess about an embolus infected with *Staph. aureus* in a dog (17) previously immunized by the intratracheal injection of a vaccine of *Staph. aureus* killed with formaldehyde. Note the relatively small area of pulmonary involvement and the absence of an abscess cavity;  $\times 9$ .

cm., whereas in the fourteen normal control animals it was 0.85 cm.

In no instance in the immune group did death result from perforation with an ensuing pleuritis.

17. Van Allen, C. M.; Cole, H., and Fox, R. A.: The Influence of Cough on the Chronicity of Lung Abscesses. *Proc. Soc. Exper. Biol. & Med.* 24:485, 1927.



The contrast between the abscesses in the two groups was as marked microscopically as grossly (figs. 4 and 5). In general, in the immunized lungs, a narrow zone of polymorphonuclear leukocytes about the embolus was surrounded by a wall of young fibroblasts. Organization of the exudate was distinctly more advanced than in the normal animals; fibroblasts were numerous and tended to encircle the embolus as the healing process advanced. The presence of the fibroblasts appeared to be independent of the existence of large blood vessels or bronchi in

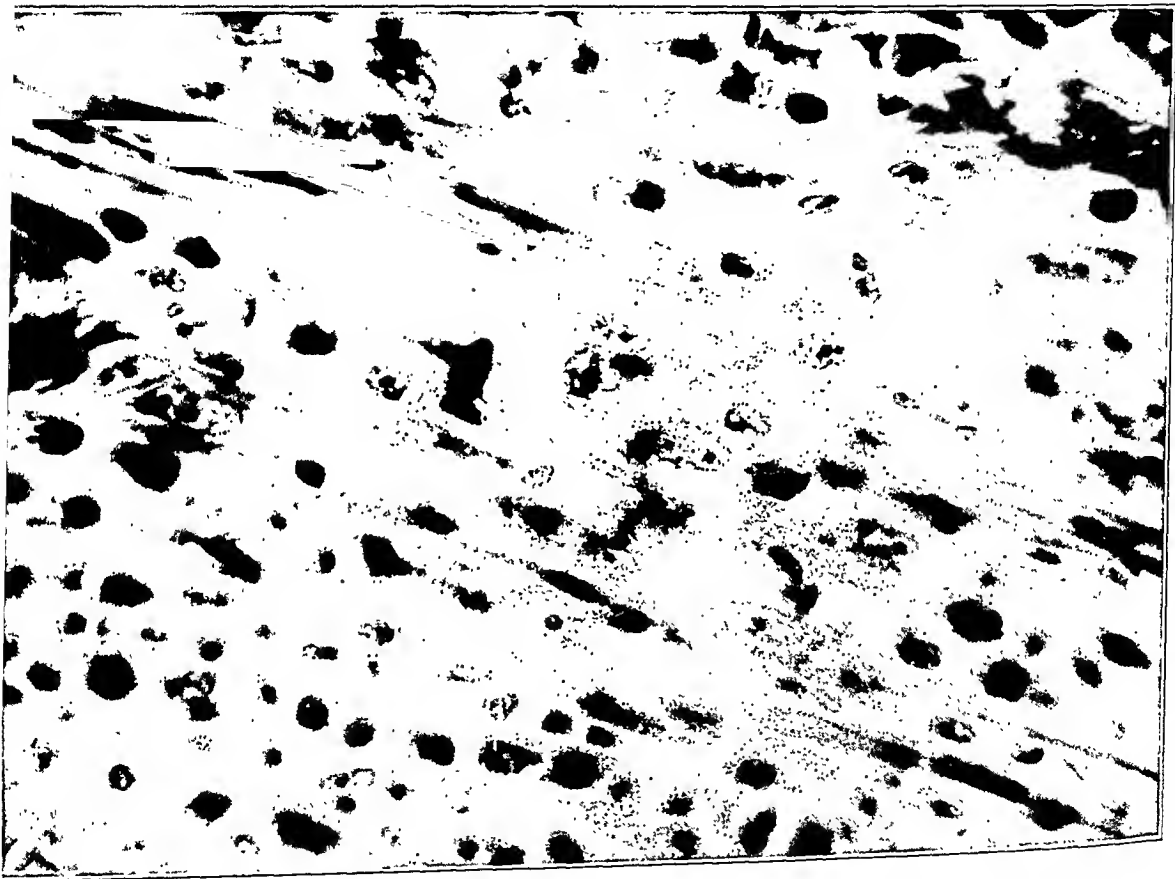


Fig. 5.—Photomicrograph of the wall of the abscess shown in figure 5. Note the fibroblastic reaction;  $\times 815$ .

the neighborhood of the embolus, suggesting that they may have arisen from macrophages.

Macrophages and large mononuclear cells, frequently containing mitotic figures, were present in greater numbers in the immune than in the normal lungs. Many of the large, foamy mononuclear cells were actively phagocytic, and a considerable number contained polymorphonuclear leukocytes and tightly packed masses of bacteria (fig. 6). In general, fewer bacteria were seen outside the embolus in the immune animals; when present, the bacteria were chiefly within the phagocytic

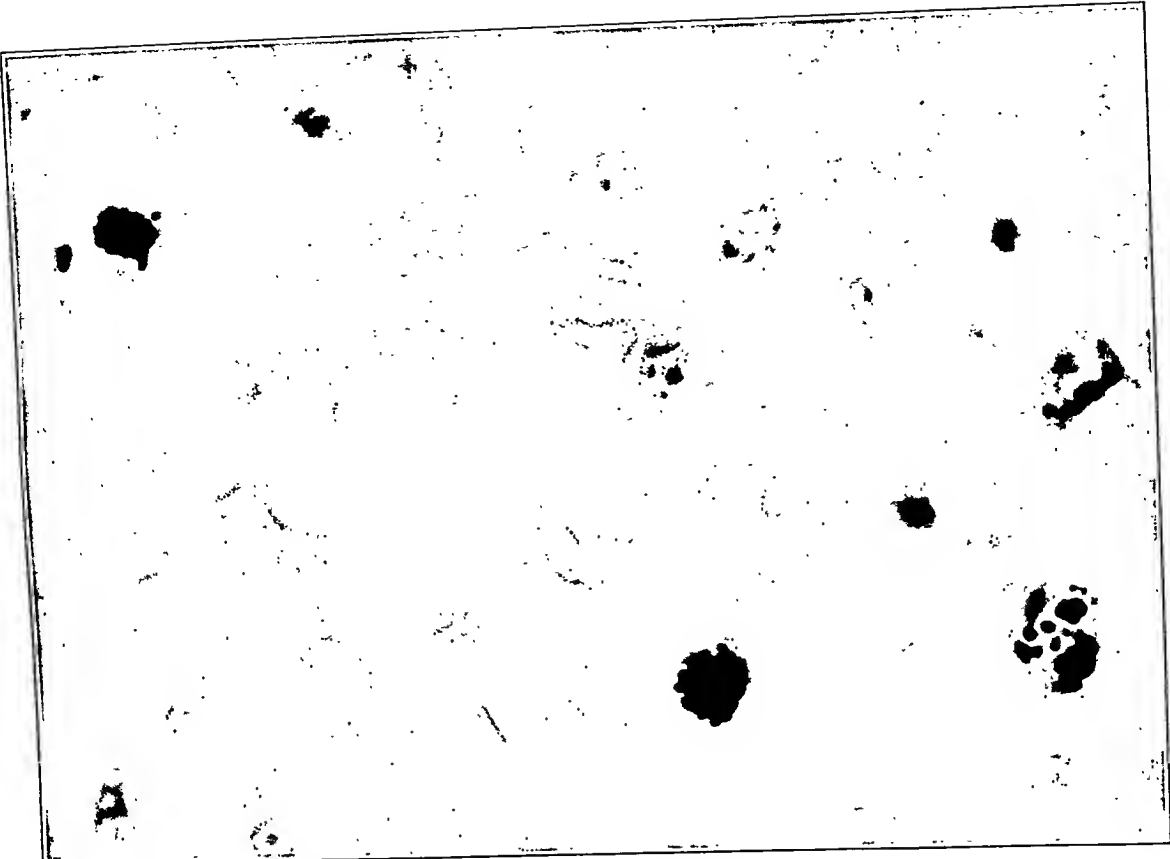


Fig. 6.—Photomicrograph showing the intracellular packing of bacteria within macrophages in the lung of an immune animal;  $\times 1,850$ .

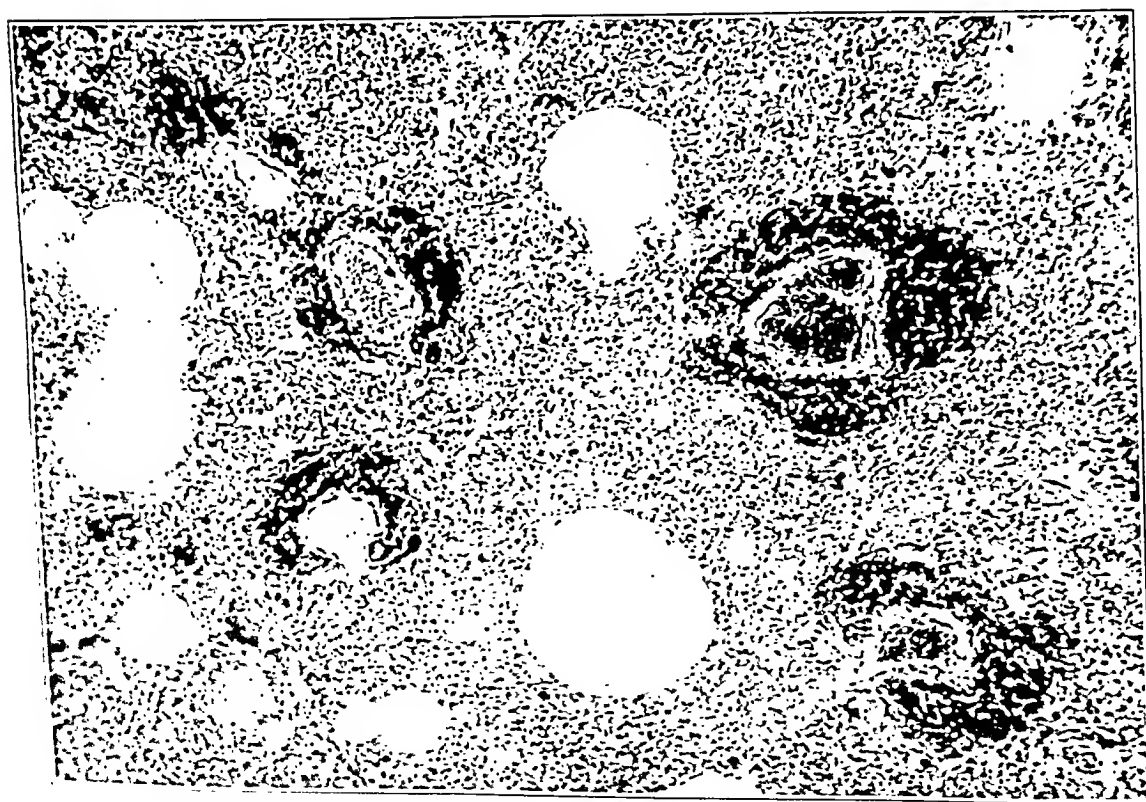


Fig. 7.—Photomicrograph illustrating the perivascular "mantling" in the tissues contiguous to the abscess in an intratracheally immunized dog;  $\times 88$ .

cells near the embolus. This packing of the bacteria into compact intracellular masses suggests an increased avidity of the macrophages for the bacteria, due presumably to a more intensive bacteriotropic action.

The "mantling" of blood vessels by the large basophilic mononuclear cells (fig. 7) was frequently seen in the inflamed tissues at a considerable distance from the embolus or abscess in the immune animals, a reaction which was regularly more marked than that which occurred in normal control dogs.

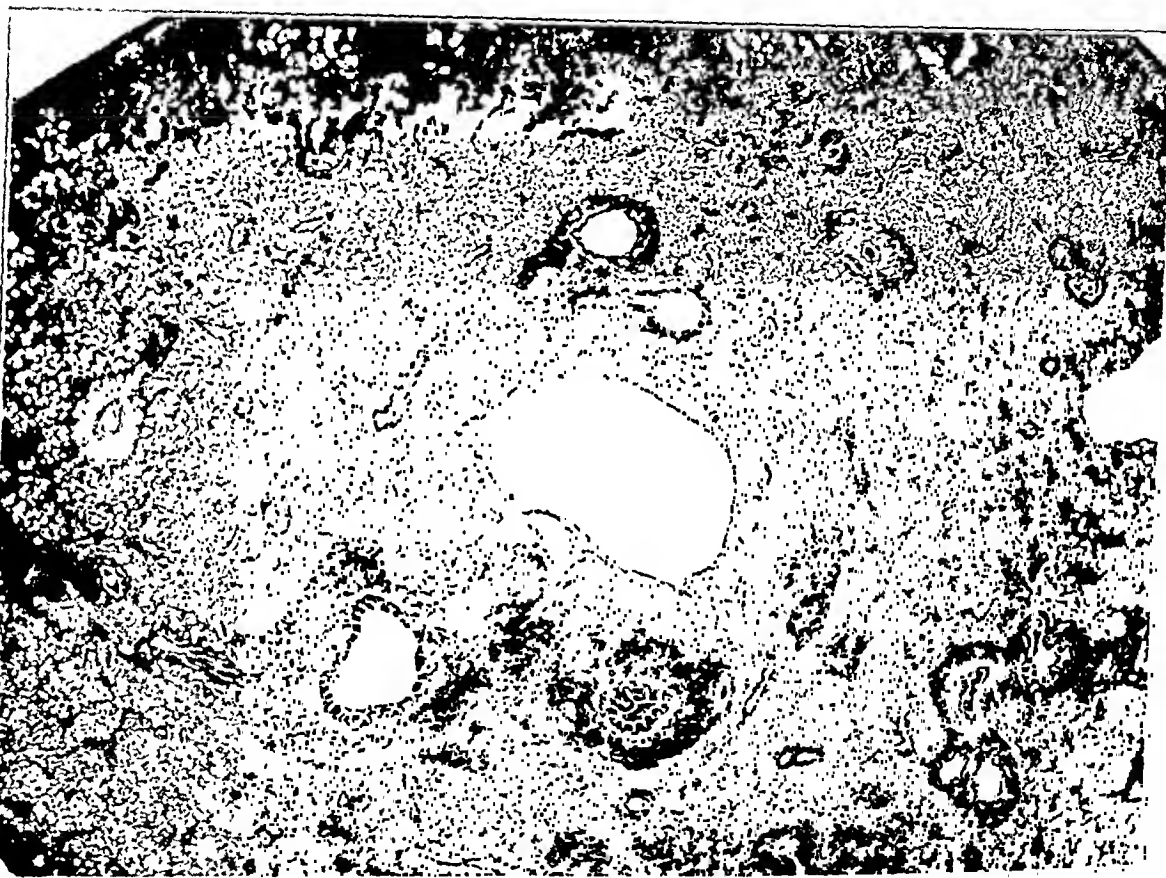


Fig. 8.—Photomicrograph of an abscess of ten days' duration in a dog (30) subcutaneously immunized with a vaccine of *Staph. aureus* and subsequently infected with an embolus containing the homologous organism. Note the diffuse consolidation of the surrounding pulmonary tissues and the relatively large abscess cavity;  $\times 6.3$ .

#### EFFECTS OF LOCAL AND GENERAL IMMUNITY ON THE DEVELOPMENT OF PULMONARY ABSCESSSES

Experiments were performed to determine if local pulmonary immunization is more effective than general immunization in restricting the development and extension of pulmonary abscesses. Five healthy dogs were immunized by the subcutaneous injection of a vaccine killed

by formaldehyde, prepared as described in the preceding pages. Dogs 29, 30 and 31 received 8 cc. of a vaccine of *Staph. aureus* killed by formaldehyde on three occasions at intervals of two days; dogs 32 and 33 received 6 cc. and 4 cc., respectively, on two occasions at intervals of two days. Normal dogs and dogs immunized intratracheally with like amounts of the same vaccine served as controls. After a period of rest following the last vaccination, which varied from forty-one to forty-five days, emboli infected with the homologous micro-organisms

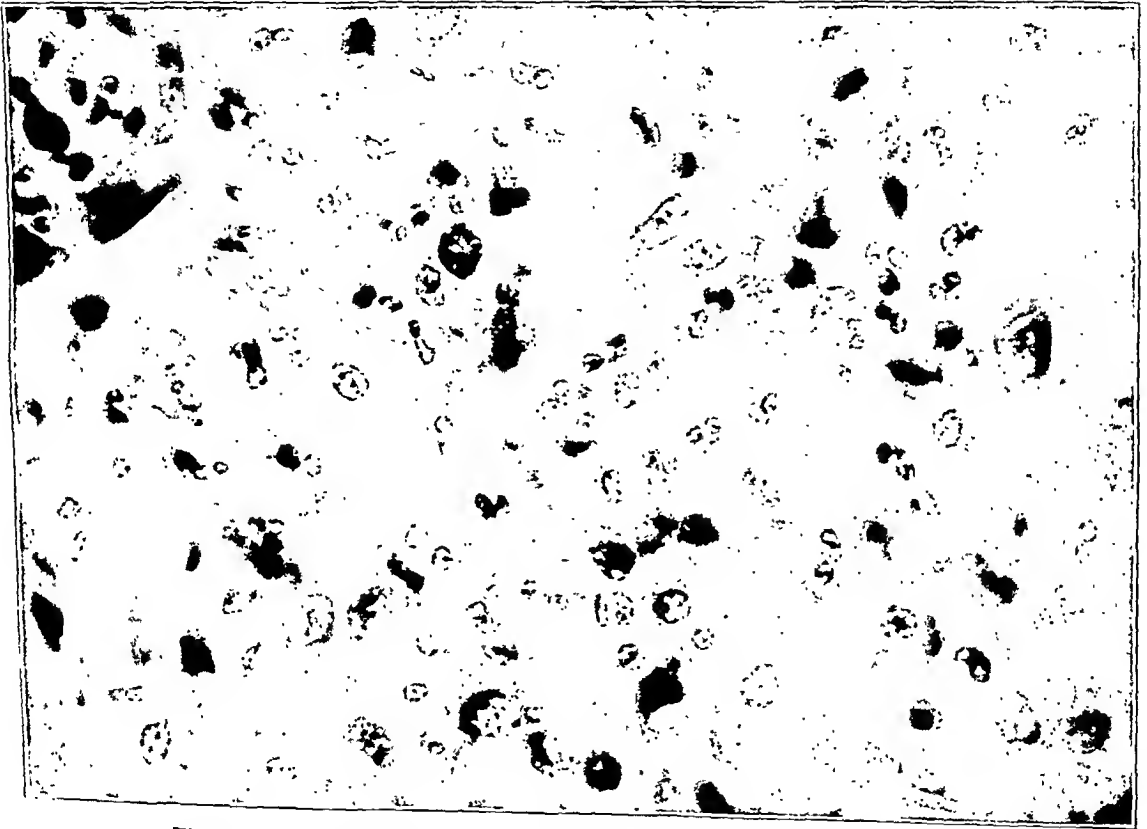


Fig. 9.—Photomicrograph ( $\times 1,815$ ) of the wall of the abscess shown in figure 8.

were introduced. The results obtained in this series are shown in table 2.

As will be seen from an examination of this table and figures 8 and 9, the tissue reactions in the subcutaneously immunized animals ranged in intensity between those of the normal and those of the intratracheally immunized dogs. Organization of the inflammatory exudate in the subcutaneously immunized animals was more vigorous than in the normal dogs, but obviously less than in the intratracheally immunized animals. Cavities were present in the lungs of all the subcutaneously

immunized animals, and in dogs 30, 31 and 33 the diameters of the cavities almost equalled those in the normal controls; this picture contrasts sharply with the small cavities, or the absence of cavities, in the lungs of the intratracheally immunized animals.

COMPARISON OF THE EFFECTS OF SPECIFIC AND NONSPECIFIC  
LOCAL IMMUNIZATION ON THE DEVELOPMENT  
OF PULMONARY ABSCESSSES

An attempt was made to determine the effects of nonspecific local immunization on the development of pulmonary abscesses. Dogs were immunized intratracheally with a vaccine of *B. coli*, and pulmonary abscesses were produced later with agar emboli infected with *Staph.*

TABLE 3.—*Comparison of the Size of the Abscess Cavity in Normal Animals and in Animals in Which Local Immunity Was Effected Specifically and Non-specifically Ten Days after Embolization*

No.	Micro-Organism in Vaccine	Route of Immunization	Micro-Organism in Embolus	Size of Abscess Cavity, Cm.	Amount of Vaccine, Cc.	Number of Vaccinations	Time of Rest Period, Days
34	<i>B. coli</i>	Intratracheal	<i>Staph. aureus</i>	0.9 by 0.5	10	2	33
35	<i>B. coli</i>	Intratracheal	<i>Staph. aureus</i>	1	10	2	33
36	<i>B. coli</i>	Intratracheal	<i>Staph. aureus</i>	0.2	10	2	33
37	<i>B. coli</i>	Intratracheal	<i>Staph. aureus</i>	0.5	10	2	33
26	<i>B. coli</i>	Intratracheal	<i>B. coli</i>	0	10	2	33
27	<i>B. coli</i>	Intratracheal	<i>B. coli</i>	0	10	2	33
28	<i>B. coli</i>	Intratracheal	<i>B. coli</i>	0	10	2	33
11	Normal	.....	<i>Staph. aureus</i>	0.8 by 0.4	..	..	..
12	Normal	.....	<i>Staph. aureus</i>	0.8	..	..	..
13	Normal	.....	<i>B. coli</i>	0.5	..	..	..
14	Normal	.....	<i>B. coli</i>	0.5	..	..	..

*aureus*. The summarized proceedings and results are shown in table 3, in which it is seen that abscesses with cavities formed in all four of the nonspecifically immunized dogs, although in one animal (dog 36) the cavity was small.

The microscopic observations on the abscesses in the nonspecifically immunized animals resembled closely those in the normal controls. The bacteria tended to permeate the surrounding tissues, even in the case of dog 36, which otherwise resembled a specifically immunized animal. Phagocytosis, although present about the abscesses, was not marked, and the cells failed to take up the large numbers of bacteria, as previously described in the cases of specifically immunized dogs. Organization of the exudate, as shown by the increased fibroblastic response, was present to a marked degree in only one animal (dog 36), whereas in the others its scarcity resembled the inertia of tissues seen in the normal control animals.

REACTION OF THE IMMUNE AND OF THE NORMAL LUNG TO A  
SEPTIC EMBOLUS IN THE EARLY AND LATE PERIODS

It was our purpose in this group of experiments to study the lesions produced by the introduction of a septic embolus into the pulmonary tissues of immune and normal control animals, both in the early stages and in the periods after ten days. An embolus infected with *B. coli* was introduced into the pulmonary artery of twelve intratracheally immunized animals which had received two injections of 6 and 4 cc., respectively, of *B. coli* vaccine at intervals of seven days followed by a rest period of twenty-one days and of twelve normal animals, and two of the first and two of the second group were killed on the first, second, third, fifth and ninth days after the introduction of the embolus. Other animals which were immunized intratracheally with the same amounts of vaccine and which had had a rest period of the same length as the animals in the groups just mentioned were killed with their normal controls on the fifteenth, twentieth, twenty-fifth and thirtieth days following embolization to permit study of the rate of healing at later periods. All of the animals were killed by electrocution, as in the previous groups, and their lungs were studied grossly and microscopically.

In the normal animals, one day after embolization, the embolus was still within the pulmonary artery, the wall of which was edematous and infiltrated with polymorphonuclear leukocytes. The surrounding pulmonary tissue was edematous, containing many red blood cells closely packed into the contiguous alveoli. Immediately about the artery a zone of polymorphonuclear leukocytes was forming, and the alveolar walls, when they were preserved, were thickened by a swelling of the septal cells. At two days, the wall of the artery was necrotic or ruptured, and polymorphonuclear leukocytes were streaming in toward the embolus through breaks in the wall. After the third day, many large macrophages began to appear in the area about the embolus, and when the embolus had lodged near a large bronchus the tendency toward a fibroblastic response was rather marked. From this time to the tenth day, the process was one of an advancing infection, with the zone about the embolus showing evidences of softening and early cavity formation, with little tendency toward an active organization of the inflammatory exudate before the ninth day.

In the immunized animals the reaction during the first four days was characterized by a larger zone of hemorrhage about the site of the embolus; as a result, the embolus was much easier to locate in the immunized than in the normal animals. When the hemorrhagic areas in the immunized animals were incised, the edema was always more intense than in the normal animals. In the later periods (from five to nine days) the zone of cellular infiltration about the embolus was grayish yellow and firmer than in the normal dogs.

Microscopically, the zone of hemorrhage and edema about the embolus in the immunized animals was conspicuous, and the greater number of swollen septal cells and large foamy macrophages in the exudate around the embolus was readily apparent. The polymorphonuclear leukocytes appeared to be much better preserved, whereas in the normal animals leukocytic fragmentation and cellular degeneration were generally present and at times marked. Fibroblasts became increasingly numerous after the fifth day.

Surprisingly, the large numbers of red blood cells within the alveoli, so prominent a feature of the early periods, had almost disappeared in both the normal and the immunized animals killed on the seventh and the ninth day.

Observations on the animals killed after ten days revealed a continuation of the process seen in the early periods. In general, in the immune animals killed on the twentieth and the twenty-fifth day the embolus was found to be surrounded by a rather dense wall of fibroblasts, while in the normal animals active inflammation was evidenced by many polymorphonuclear leukocytes, small cavities and a fibroblastic ingrowth less abundant than that seen in the immune animals.

It may be said, then, that the response of the lungs of immune animals in the early period, in which the reaction was exudative, and in the later period, in which it was primarily a reaction of healing, was always more marked than that in the lungs of untreated animals.

#### COMMENT

The theoretical bases underlying these experiments justify detailed analysis, as the facts tend to substantiate further the validity of the original assumption that differing levels of pulmonary resistance may be secured by appropriate immunologic devices.

The anatomic nature of the pulmonary alveoli, with the intimate relationship of the air to the blood stream, suggests the presence of a barrier permeable to gases and fluids but impermeable to inhaled particles. Figure 10 reveals the mechanism of this barrier in the lung of a dog into which living staphylococci had been introduced through the trachea approximately seventy-five minutes before. The entrapping of the bacteria by the septal cells both while they were attached and while they were detached, associated with the adherence of bacterial particles to the interalveolar reticulum, affords considerable evidence of the manner in which particles are prevented from invading the blood stream.

The further fate of the bacteria is probably closely linked with that of the septal cells. The coughing up and expulsion of these cells should eliminate the bacteria within them, but it is improbable that under ordinary conditions a considerable number of septal cells are disposed of in this way. Their morphologic resemblance to macrophages elsewhere in the body suggests that they may also participate in the formation of

antibodies through their digestion of engulfed bacterial particles. Such locally formed antibodies should therefore permeate the pulmonary tissues as well as diffuse into the lymphatics and the blood stream. The experiments of Cannon and Sullivan<sup>18</sup> indicate that the concentration of locally formed antibodies in tissues may vary considerably, being greatest in the tissues into which the antigen is introduced. Under



Fig. 10.—Photomicrograph of a drawing made with the aid of a camera lucida of a section from the lung of a normal dog seventy-five minutes after the intratracheal introduction of a suspension of staphylococci. Note the engulfment of the cocci by septal cells and the adherence of clumps of bacteria to the septal wall.

the conditions of our experiments, therefore, a greater concentration of antibodies might be expected in the pulmonary tissues, whence they would tend to diffuse gradually into the blood and lymph streams in

18. Cannon, P. R., and Sullivan, F. L.: Local Formation of Antibody by the Skin, *Proc. Soc. Exper. Biol. & Med.* 29:517, 1932.



the process of generalized passive immunization. There is no direct proof, however, that such local formation of antibodies occurs in the lungs, although study of this problem is now in progress. Furthermore, any antigen which passes the primary pulmonary epithelial barrier during the course of intratracheal immunization causes development of a generalized active immunization concomitantly with the development of a local pulmonary immunity.

The introduction of a foreign protein of particulate nature into the lungs stimulates the tissues to cellular proliferation, and the actual increase in the number of immature basophilic mesenchymal cells in an irritated lung of this sort presumably results from such a stimulus. The later differentiation of these cells into functionally mature macrophages, from the direct proliferation of septal cells in the septal wall, from the emigration of monocytes from the blood stream into the alveolar septum or from the proliferation of undifferentiated cells in the adventitia of the blood vessels, provides increased numbers of phagocytic cells for reaction to further injury. This enlarged reservoir of phagocytic cells, therefore, by engulfing antigenic particles and possibly by liberating specific antibodies into the pulmonary structures, should serve to elevate the level of resistance of the lungs to subsequent infection with the homologous living micro-organism.

What is the most probable effect of an increased concentration of antibodies in these tissues? According to Rich,<sup>19</sup> antibodies in tissue increase the adhesion of the homologous bacteria to the tissue and to one another, thus limiting the extent of their "drift" through the tissues. In this way infection remains localized and less serious than if it was the consequence of a generalized dissemination of the bacteria. The experiments of Cannon and Pacheco<sup>20</sup> pointed in the same direction and placed a further emphasis on a more efficient bacteriotropic action in the facilitation of phagocytosis, thus favoring both the immediate and the continued localization of the invading bacteria. In whatever manner the bacteria are fixed, it is obvious that in pulmonary infection the degree of dissemination in the blood stream will vary inversely with the initial ability of the lungs to fix the bacteria effectively and with the facility with which the phagocytic septal cells and polymorphonuclear leukocytes engulf and destroy them.

In our experiments, the lungs are probably at a more marked disadvantage than under conditions of natural infection, for whereas in infection by aspiration the infectious agents come into direct and immediate contact with the pulmonary tissue and cellular barriers, this contact is

---

19. Rich, A. R.: *The Prevention of Spread of Bacteria in the Immune Body*, Bull. Johns Hopkins Hosp. 52:203, 1933.

20. Cannon, P. R., and Pacheco, J. L.: *Studies in Tissue-Immunity: Cellular Reactions of the Skin of the Guinea Pig as Influenced by Local Active Immunization*, Am. J. Path. 6:749, 1930.

delayed for twenty-four hours or more when the infection follows embolization of a pulmonary artery. During this period the bacteria may grow within the embolus, protected to a large extent against leukocytic infiltration by the wall of the pulmonary artery. Furthermore, embolic obstruction of the artery should seriously disturb the normal pulmonary architecture because of the resulting circulatory interference. Therefore, locally mobilized phagocytes and a locally increased concentration of antibodies are of little avail, presumably, until the wall of the pulmonary artery has been eroded and direct contact between the bacteria and the defensive elements of the body has been established. Furthermore, chance localization of an infected embolus near the pleural surface or a large bronchus, especially if the condition is complicated by undue coughing, may interfere seriously with defensive reactions which under more favorable conditions would be adequate. Consideration of these adverse possibilities, therefore, makes the sharp contrast in the tissue reactions in these experiments the more remarkable.

The evaluation of the comparative effects of local versus general immunization is also highly important. The possibility of elevating the local pulmonary defenses to the point of practically closing a portal of entry justifies exploration of these local immunizing procedures. Local concentration of antigen within the lungs can best be secured by its intratracheal deposition and retention; this is not possible if the antigen is introduced in any other way, i. e., intravenously or subcutaneously, as most of it passes through the lungs and eventually localizes in the liver and spleen. Thus the principal immunologic benefits to the lungs which occur later come indirectly from the presence of protective antibodies in the blood stream and then in too dilute concentrations to be quickly effective in a local infection of the lung. Theoretically, both local and general immunization are indicated, but prophylactically, local methods deserve greater consideration because of the possibility that these immunized tissues may be better able to meet a threat of infection quickly and effectively.

The problem of specificity also deserves consideration. Our experiments, although few, offer no encouragement to the view that nonspecific immunization is as effective as specific measures in elevating the reacting capacity of the tissues. Specificity is a principle of immunology which has stood the test of time well, and it probably should be given primary consideration whenever it is practically possible to do so.

The presence of antibodies in the lungs of the immunized dogs was not determined directly by serologic procedures, but suggested by the morphologic observations. A surprising feature was the ability of the bacteria to grow in the agar emboli in the immune tissues, in which the colonies formed and grew, not in the depths of the agar farthest away from the possible effects of bactericidal antibodies, but at the edge of the embolus nearest to the tissue fluids (fig. 11). It is obvious,

therefore, that the killing effects of these antibodies were not conspicuous *in vivo*. No agglutination of bacteria, as described by Cannon and Pacheco in the skin of guinea-pigs locally immunized against staphylococci, was observed. The greater numbers of bacteria within the phagocytes in the immune dogs and their tendency to become packed together until the outlines of the cell bodies were no longer discernible suggest an enhanced bacteriotropic action in the lungs of the locally immunized animals.

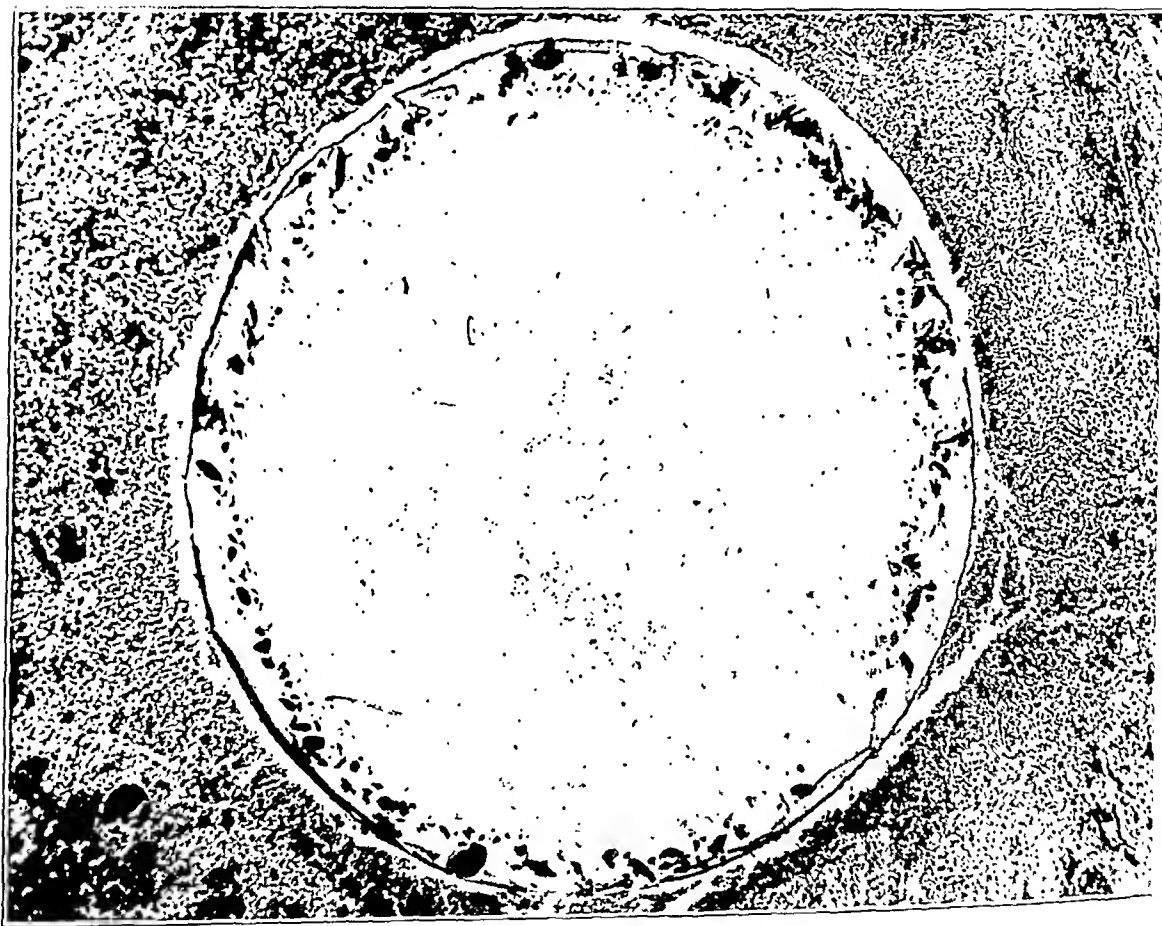


Fig. 11.—Photomicrograph of a cross-section of an agar embolus within a locally immunized lung. Note the bacterial colonies at the periphery of the embolus and their absence in the center;  $\times 36$ .

The significance of the increased numbers of basophilic mononuclear cells forming "collars" around the blood vessels is probably of more theoretical than practical importance. If our assumption is correct that this indicates a mesenchymal activation by which large reserves of functionally active potential phagocytes become available, it is not so important whether they arise *in situ* or by migration of monocytes from

the blood stream. The sharpness of the outer edges of the "collars" and the frequency of mitoses, however, incline us to the view that many of these cells arise in situ from the undifferentiated cells of the adventitia of the blood vessels and therefore correspond to the adventitial cells described by Marchand. It should be added, however, that increased numbers of monocytes are present in the lumens of the blood vessels, and that these also are probably leaving the blood stream constantly.

#### SUMMARY AND CONCLUSIONS

The effects of local, general and nonspecific immunization on the course of development of experimental pulmonary abscess in the dog were determined. Dogs were immunized subcutaneously and intratracheally with vaccines of *Staph. aureus* or *B. coli* killed with formaldehyde; later, pulmonary abscesses were produced by the introduction into the external jugular vein of an agar embolus containing living staphylococci or colon bacilli. Ten days later, as a rule, the pulmonary abscesses were examined grossly and microscopically as to the size, the formation of cavities and the state of healing. The general results may be summarized as follows:

1. Abscesses in intratracheally immunized dogs were, in general, smaller, more circumscribed and less subject to the formation of cavities than those in normal or subcutaneously immunized animals.
2. Organization of the inflammatory exudate developed much more rapidly in the intratracheally immunized dogs than in the normal or the subcutaneously immunized dogs.
3. The infecting bacteria remained more localized in intratracheally immunized animals and were engulfed in larger numbers by pulmonary phagocytes.
4. Local pulmonary immunization was superior to general immunization in facilitating the circumscription and healing of the abscesses produced.
5. Specific immunization was more effective than nonspecific immunization in restricting the development and extension of pulmonary abscesses in the dog.

# EPITHELIOMA FOLLOWING AVULSION OF THE SCALP

REPORT OF A CASE

EDWARD L. BURNS, M.D.

ST. LOUIS

Two types of avulsion of the scalp, complete and incomplete, are generally recognized. Complete avulsion defines those cases in which part or all of the scalp is torn entirely free from its attachments. The incompletely avulsed scalp is left attached to some part of the head by a pedicle.

At present, complete avulsion is almost always exclusively the result of an industrial accident. It occurs chiefly in manufacturing plants where rapidly revolving shafts and wheels are used and more particularly where such moving parts are inadequately housed. The hair becomes caught in the whirling machine, and a sudden force, quickly transmitted, removes the scalp. Because of this mode of occurrence the accident is limited almost entirely to women. Avulsion of the scalp occurs frequently with farm machinery also; a few scalps have been lost by burning; in frontier days scalping by Indians was encountered, and other isolated and bizarre methods have been reported.

Usually the scalp separates in the fatty layer of tissue between the aponeurosis of the occipitofrontalis muscle and the periosteum of the skull, and often the denuded area extends from the eyebrows in front to the occiput posteriorly. Cases have been reported in which all the periosteum was torn away, and it is common to find small localized periosteal defects.

Such an extensive wound is often unassociated with serious immediate complications. Pain, hemorrhage and shock, although sometimes severe, seldom lead to death and are often either mild or absent. In some instances the patient has been unaware of the accident until placing his hands on the denuded head, and it is not uncommon for a patient to walk to the physician's office or to travel a long distance to obtain help.

Later complications often prolong healing and therefore make scalping a dangerous mishap. Infection occurring at the time of the accident may remain limited to the surface of the wound, extend into the bone

---

From the Department of Pathology, Washington University School of Medicine, and Barnes Hospital.

to produce osteomyelitis or penetrate the skull along venous channels to initiate meningitis or abscess of the brain. Hemorrhage and pain, although absent at first, are often troublesome complications later. Exfoliation of the bone usually occurs when there are large periosteal defects. If the wound is allowed to epitheliate spontaneously, formations of scar tissue produce marked retraction deformities. Most serious among the latter is the mild or marked ectropion which may occur in cases in which the line of tearing included the eyebrows or eyelids. Later, ulcers are prone to develop in the newly epithelialized or grafted areas. Many other unusual complications are reported.

In treating patients with complete avulsion, it is useless to replace the avulsed scalp, since it invariably sloughs away. However, early skin grafting in some form prevents later complications from scar tissue retractions. Heterogeneous and even homogeneous skin grafts are unsuccessful, whereas autoplasmic grafting gives satisfactory results. Granulations may be secured to cover denuded bone by boring through the outer table of the skull. More specific forms of treatment, outlined by many authors, are beyond the scope of this article.

The mortality from complete avulsion is from 8 to 20 per cent according to various authors. Davis, in a thorough review of cases reported up to 1911, found eight deaths in eighty-five instances of complete scalping. In fifty-three cases reported since that time which I have reviewed the mortality was calculated to be 7.5 per cent. However, the final result was not given in some of the reports.

Incomplete avulsion, in contradistinction to the complete form, is seldom caused by accidents with rotating machinery. Glancing blows on the head, falls, scraping under wheels and other mishaps encountered in the general walks of life account for most cases of this kind.

As might be surmised, the type and extent of the wounds of incomplete avulsion are varied. Occasionally the entire scalp from the eyebrows to the occiput may remain attached only to a pedicle anteriorly or posteriorly, but more frequently the wound is of smaller extent.

When the partially avulsed scalp is sutured into place, healing occurs rapidly if the pedicle by which the denuded flap is attached carries an adequate blood supply. For this reason incomplete scalping is a much less serious accident and is seldom followed by the complications and difficulties seen after complete avulsion.

The following report concerns a fatal case of complete scalping, remarkable for the complications which followed and for their late appearance.

#### REPORT OF CASE

*History.*—A. D., a white woman, aged 34, was admitted to Barnes Hospital on Jan. 11, 1928.

No relevant facts were found in either the family or the personal history. Her present illness began in 1907, twenty-one years previous to admission, when, while working in an underwear factory, her hair was caught on a revolving shaft. The scalp was completely avulsed. The two terminal phalanges of a second finger and an entire index finger were torn away at the same time. Profuse bleeding and shock occurred at the time of the accident, but there was no loss of consciousness. The patient stated that there was no fracture of the skull, although she thought the bone was injured. No roentgenograms were made.

Immediately after the accident the avulsed scalp was sutured in place, but it sloughed off in a few days. During the first eleven days of the two months spent in bed, there was high fever. Six months after the casualty, a single unsuccessful attempt was made to graft skin, taken from the thigh of the patient's mother, on the denuded area. Following this operation, the wound was allowed to heal by spontaneous epitheliation, a process which required sixteen years for completion. It was accomplished in 1923.

Meanwhile, in 1918, the patient married. In 1924 she became pregnant and was successfully delivered of a normal girl. Shortly before the birth of the child, a shallow ulcer, about  $1\frac{1}{2}$  inches (3.8 cm.) in diameter, formed over the vertex of the skull. There was little discharge from the area, and it was considered of no consequence. Subsequent healing and reappearance of the ulcer occurred, and at times the recurrent ulcerations were associated with a discharge of purulent material. Otherwise the patient was well until the birth of her second child in 1928, six months previous to her admission to the hospital.

Shortly before the delivery of the second child, it was noted that the ulcer formed a "hole" about  $\frac{3}{4}$  inch (1.9 cm.) deep in the top of the head. Dull and constant but rather mild pains occurred in the forehead and temples and sometimes in the face. The pains increased in severity and sharpness and became shooting. At the same time, the purulent discharge increased. On Jan. 11, 1928, the patient came to the outpatient department of Washington University and was admitted to Barnes Hospital.

*Physical Examination.*—Examination revealed an active, alert woman in no apparent discomfort, with a good memory and no defects of speech. A foul odor was noted.

A wig was worn, and its removal disclosed a large scar covering the top of the head. The margin of the scarred area formed a circle about the calvarium. In front it ran diagonally across the forehead from left to right somewhat below the hair line. Laterally it crossed each temporal region about 2 inches (5 cm.) above the ears, and posteriorly it extended just below the occipital protuberance. On the right side there was an extension of the scar over the zygoma and down onto the cheek. A thin rim of hair remained about the sides and back of the head.

In the middle of the large scar, at the junction of the parietal and occipital bones, was an ulcer measuring  $1\frac{1}{2}$  inches in diameter. The margins of the ulcer were composed of granulation tissue which surrounded a base of black, dead-looking bone. In the center of the crater the dura was covered with a small amount of granulation tissue and some pus. At this point the ulcer was about  $\frac{1}{2}$  inch (1.2 cm.) deep.

The scar over the right eye had pulled the eyebrow about an inch above its normal position and laterally. The vision in both eyes was good. The right pupil was slightly larger than the left, but both were round and regular in outline and reacted to light and in accommodation. There was no nystagmus, and ophthalmoscopic examination revealed normal eyegrounds.

A careful systemic and neurologic examination disclosed nothing of importance.

A diagnosis of osteomyelitis of the skull was made. Surgical solution of chlorinated soda was applied to the wound, and much of the necrotic bone was removed with forceps.

*Course.*—During the first three months of the patient's stay in the hospital, efforts were made to cause spontaneous healing of the ulcer. Surgical solution of chlorinated soda and petrolatum and mercurochrome dressings were used to combat the infection. Under such treatment the wound improved; in about two months it appeared to be fairly clean but showed no tendency to heal. Microscopic examination of tissue removed from the margin of the ulcer revealed marked proliferation of the epithelium and pearl formation, associated with round cell infiltration. The process was considered to be one of chronic infection rather than one of malignant character.

Because infection persisted and the wound failed to heal, it was decided, three months after the patient's admission, on April 12, to excise the infected area. Bone and soft tissue were removed for  $1\frac{1}{2}$  inches about the margin of the ulcer. The patient gradually recovered from the operation, and two months later, on June 16, the wound was considered in condition for grafting. During this time there was occasional headache on the right side which extended down onto the right side of the face.

On June 16 a flap from the left lower portion of the abdomen was attached to the left forearm. On November 21 it was raised and transferred to the head. A week later infection supervened, and the graft was removed from the head and folded on itself on the arm. Attention was again turned to making the wound clean.

Meanwhile, biopsy sections taken from time to time showed marked hyperplasia, apparently due to chronic inflammation.

On Jan. 24, 1929, the patient had a localized convulsion and fainted. On February 10 she fell while going to the bathroom. The following day she grew comatose, with the temperature 40 C. (104 F.) and the pulse rate 140 per minute. Spinal puncture showed a cloudy fluid. Gram-positive organisms were found in a smear from this material, and culture showed hemolytic streptococci. Drainage was established by means of a laminectomy. That evening the patient was moribund. On the following day, February 12, the temperature rose to 41.8 C. (107.2 F.) and the breath was gasping. The heart and respiration failed simultaneously, and the patient died. An autopsy was performed two hours after death.

*Autopsy.*—On the surface of the body were the scars produced by the plastic operation described. The abdominal flap remained attached to the left arm by a pedicle.

On the head was a large scarred area, the center of which was ulcerated. The outer margins of the scar extended from over the right eye to the occipital protuberance and laterally to about 2 inches above each ear. Thin skin covered only the outer portion of the area, while the center was occupied by a large infected ulcer which measured about 15 cm. in diameter and covered the top of the calvarium. Its somewhat elevated surface was composed of grayish, swollen, foul-smelling granulation tissue. Pus covered some regions. From beneath the ulcer, portions of the frontal, parietal and occipital bones had been removed so that the soft tissues were compressible from the outside.

*Brain:* The infected granulating ulcer was clipped away and removed with the brain. It was intimately attached to the dura, and over the right cerebral hemisphere it was attached to the substance of the brain itself. The falx cerebri was thickened. A heavy coat of yellow purulent exudate surrounded the base of the brain and extended over the under surfaces of the cerebellum and temporal lobes.



The brain and the attached granulation tissue were hardened in a dilute solution of formaldehyde before cutting. Sections made through the frontal lobes showed the infected ulcer closely adherent to the dura and cortex on the right side. Beneath this area a strip of darkened, softened brain tissue led to the cavity of a large abscess which measured about 4 by 5 cm. and occupied portions of the right frontal and parietal lobes (fig. 1). It was filled with thick purulent material and was lined with rough, dark, necrotic-looking tissue. For some distance about the abscess the brain tissue was softened and discolored, and in one area, where the cavity lay in close relation to the lateral ventricle, extension of the infection into the anterior horn had occurred. The ependymal lining was dull, roughened and covered with a thin layer of exudate. Sections made through the remainder of the brain showed no other lesions.



Fig. 1.—Section of the brain at the level of the abscess. The covering of malignant, infected granulation tissue is shown attached to the upper surface of the right cerebral hemisphere. Necrotic brain tissue extends from this point to the cavity of the abscess. Distortion of the ventricular system is apparent.

**Viscera:** Examination of the abdominal and thoracic viscera revealed few changes of importance. There were healed tuberculous foci in the upper lobe of the left lung and in the middle lobe of the right lung. The spleen weighed 315 Gm. and was dark red, and the pulp was somewhat softened.

**Scalp:** Microscopic examination of section 1, taken from the healed border of the scarred area, revealed a connective tissue base over which stratified squamous epithelium had grown. The epithelium appeared to be normal, but toward the edge of the scar it was thinned to a narrow layer, 1 or 2 cells in thickness. Beyond this area were a few islands of epithelial tissue on the surface of the wound. No evidence of malignant transformation was found in this section. The connective tissue beneath the epithelium was rather dense, with an abundance of pink-staining

collagenous material. Many lymphocytes and large mononuclear cells and some plasma cells were found between the connective tissue strands, and the number increased as the margin of epithelization was approached.

Section 2 was taken from the center of the ulcer. The outer surface was covered with a pink-staining, amorphous, necrotic exudate mixed with a small amount of fibrin and numerous blue-staining clumps of bacteria. Remnants of epithelial cells were prominent in this layer. In some areas lymphocytes and swollen macrophages were found beneath, as well as in, the layer of necrotic debris, while in other parts dense accumulations of polymorphonuclear cells and bacteria were present, especially at the sites where the tissue, on gross inspection, appeared to be infected.

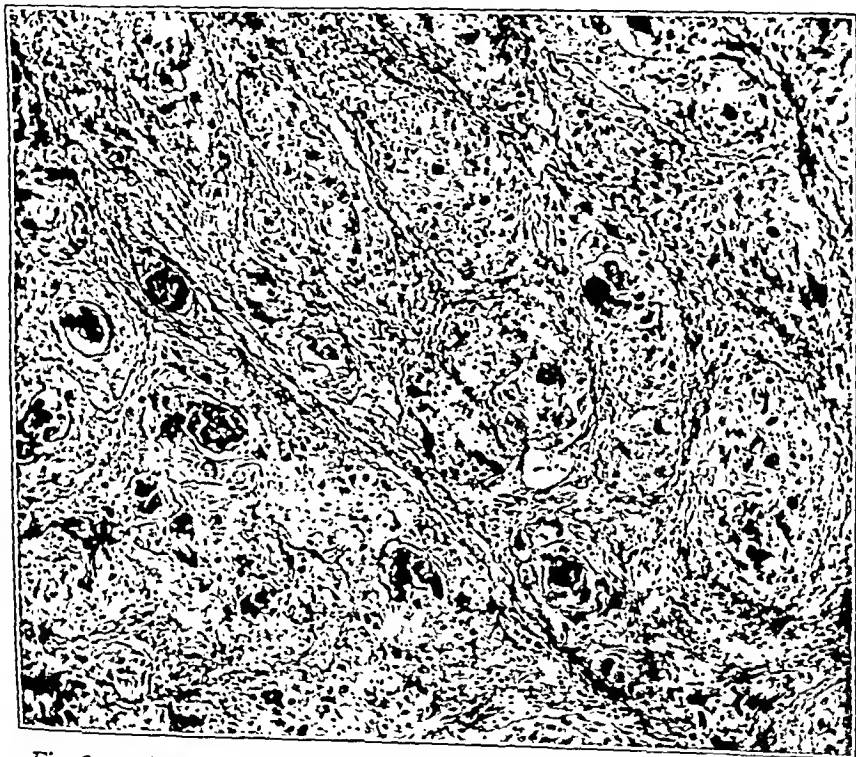


Fig. 2.—This section is *A* in figure 1, from below the ulcerated surface of the scalp. Flat sheets and nests of malignant epithelial cells are shown lying in a loose connective tissue stroma. Lymphocytic infiltration of the stroma is marked.

These more superficial layers merged gradually into the deeper tissue, where there was a malignant proliferation of epithelial cells. An abortive attempt at epithelization was found in some of the cracks and crevices on the surface of the ulcer, but beneath such areas the cells extended directly into the tissues below. Here, in the deeper layers, epithelial tissue had grown in disorderly anastomosing strands, flat sheets, solid masses and isolated islands (fig. 2). The cells were large and swollen, and some were in the process of mitotic division. Where they had become separated from the peripheral blood supply they had invariably degenerated, and appeared as swollen, pink, hyalinized cells with pyknotic or faintly staining nuclei. In the center of epithelial nests, the typical pearl formation of squamous

carcinoma was noted. Some of the keratinized areas were undergoing solution, and many polymorphonuclear and large mononuclear cells were seen in their central parts.

Between the strands of malignant epithelial tissue ran a rather loose connective tissue stroma which was densely infiltrated with lymphocytes and macrophages and a few polymorphonuclear cells.

Brain: Section 1 was taken in order to study the relation of the brain to the infected granulating wound on the surface and the extension of the infection from this site to the abscess of the brain. A portion of the wall of the abscess was included.

The outermost portion of the section thus showed a thin strip of tissue similar to that described as present in the section of the scalp. Beneath this layer was



Fig. 3.—This section is *B* in figure 1, a portion of the wall of the abscess of the brain lined with squamous epithelium. Invasion of the brain tissue by malignant cells has occurred beneath this lining.

the region occupied by the meninges. Only remnants of those structures, marked chiefly by blood vessels, remained. In most places, connective tissue and epithelial cells had invaded and obliterated the dura and pia-arachnoid and were in direct contact with the brain. Some epithelial cells had grown for a short distance into the cortex. In other areas dense accumulations of polymorphonuclear leukocytes, with fibrin and much necrotic debris, occupied the region of the subarachnoid space. At such sites the walls of many blood vessels were surrounded and invaded by inflammatory cells. Necrosis and rupture of some vessels, apparently veins, had produced small hemorrhages into the exudate. Blue-staining clumps of bacteria were prominent everywhere.

Beneath the portion just described the brain substance was destroyed almost beyond recognition. Extension of polymorphonuclear cells into the cortex had occurred, especially about numerous dilated blood vessels, but there was also a diffuse infiltration of the intervening tissue. In some areas, collections of these cells and the solution and disappearance of nerve tissue had progressed to the formation of small abscesses. Few living nerve cells were found; in most places the cells had vanished, leaving only neuroglia and large mononuclear phagocytes, while in other regions they contained pyknotic nuclei and shrunken, granular, pink-staining cytoplasm. The path of infection could thus be traced deep into the brain substance, where it became localized about the abscess.

The wall of the abscess was lined irregularly with dense accumulations of polymorphonuclear and large mononuclear cells, the cytoplasm of the latter being distended by ingested material. Broken remnants of neuroglia were observed between these cells, and blood vessels persisted far out into the necrotic wall. Some of the blood channels were completely destroyed, and their remains appeared as pink, hyalinized structures; others showed beginning invasion of their coats and thrombosed lumens. Occasionally, accumulations of red blood cells and fibrin marked the site of hemorrhage from one of these vessels.

Epithelial cells, similar to those described as occurring on the surface, were found in the abscess cavity. Most of them were necrotic, and their degenerated remains suggested that they had preceded the infection to the site of the abscess. In other places epithelial cells lined the wall of the abscess (fig. 3). Other groups had invaded the brain substance, where in some cases they formed pearls. However, no continuity with the carcinoma cells on the surface could be established in this section.

The destruction of the nerve tissue extended for some distance about the wall of the abscess and many active mononuclear phagocytes had wandered into these areas. Still farther away, small localized hemorrhages had occurred, and occasionally groups of polymorphonuclear cells were found.

Section 2 was taken in order to study the extension of infection from the abscess toward the lateral ventricle. At one point there were necrosis and solution of the ventricular lining with the extension of an exudate of polymorphonuclear leukocytes into the ventricular cavity. The relation of this invasion to the abscess could not be clearly demonstrated at this level.

#### COMMENT

The late onset of fatal complications and their character make this case unusual. Osteomyelitis, meningitis and abscess of the brain have all been reported following avulsion of the scalp, but they are usually coincident with the acute infection which often immediately follows the accident. That they may result indirectly from scalping twenty-one years after its occurrence is interesting. Such a fact suggests that cases in which the patient is reported as recovered when epitheliation is complete may later show complications. Thus complete avulsion of the scalp may be an even more formidable accident than the records of cases indicate.

The development of an epithelioma in tissue first stimulated to proliferation by a large surface defect and later by infection is interesting but not unusual. It is well known that any chronic ulcer may

become the seat of a cancer (Graham) and that many forms of physical and chemical irritation may produce epithelioma of the skin (Ewing). Loeb, in discussing the etiology of cancer of the skin divided the irritating agents into two groups, internal and external. While both factors are present in the majority of cases, as a rule one or the other predominates. In certain cases only internal factors and in others only external factors are noticeable. Thus in cases of xeroderma pigmentosum some internal factor makes the skin peculiarly susceptible to the action of ultraviolet rays, while the development of cancer from exposure to roentgen rays seems to depend almost entirely on external stimulation. In the case reported here the external irritating agencies played the most important rôle in producing a malignant tumor.

It is not uncommon, of course, for an abscess of the brain to result from the extension of a surface infection along venous channels. In this case, however, at the time of autopsy, direct growth of tumor cells across the meninges and through the brain substance was established. From the histologic study it seems probable that these cells preceded and marked the path of infection which developed later.

#### SUMMARY

A case of complete avulsion of the scalp is reported in which the sequence of events was as follows: (1) spontaneous epitheliation over a period of sixteen years; (2) subsequent ulceration and infection of a portion of the healed area during pregnancy; (3) development of osteomyelitis of the skull, which later necessitated removal of the top of the calvarium; (4) failure in attempts at plastic repair, and (5) death with symptoms of meningitis twenty-one years after the accident.

Autopsy revealed: (1) an epithelioma growing in the infected granulating wound of the scalp and invading the brain substance, the development of which was evidently due to the long continued overstimulation of the actively regenerating epithelium contained in the ulcer; (2) an abscess of the brain partially filled with carcinoma cells, communicating with an infected area of the surface and at one point ruptured into the right lateral ventricle, and (3) acute meningitis.

Dr. H. A. McCordock made the photomicrographs.

#### BIBLIOGRAPHY

##### GENERAL

- Ewing, James: *Neoplastic Diseases*, Philadelphia, W. B. Saunders Company, 1928, p. 864.  
 Graham, E. A.: *Surgical Diagnosis*, Philadelphia, W. B. Saunders Company, 1930, vol. 2, p. 178.  
 Loeb, Leo: *Etiology of Cancer of the Skin*, J. A. M. A. **55**:1607 (Nov. 5) 1910.

CASES OF COMPLETE AVULSION

- Banks, A. G.: *Brit. M. J.* **2**:893 (Nov. 17) 1928.  
 Bellantoni, R.: *Lancet-Clinic* **99**:216, 1908.  
 Berard and Cotte: *Lyon méd.* **122**:540, 1914.  
 Brookes, W. L.: *Indian M. Gaz.* **61**:128, 1926.  
 Byron, R. L., and Carter, W. E.: *South. California Practitioner* **28**:469, 1912.  
 de Carpentries: *Bull. et mém. Soc. de chir. de Paris* **40**:1074, 1914.  
 Case: *Indian M. Gaz.* **18**:43, 1883.  
 Chepmell, I. D.: *Lancet* **1**:76, 1913.  
 Davis, J. S.: *Johns Hopkins Hosp. Rep.* **16**:257, 1911 (ninety-two cases).  
 Davison, T. C.: Replacement of Scalp on a Denuded Dry Skull by Granulations Secured Through Holes Drilled in the Bone, *J. A. M. A.* **70**:1368 (May 11) 1918.  
 Decourteix: *Ann. Soc. de méd. de St. Étienne et la Loire* **5**:522, 1872.  
 Douglas, R.: *Chinese M. J.* **40**:463, 1926.  
 Düttman, E.: *Deutsche med. Wchnschr.* **49**:1438 (Nov. 16) 1923.  
 Flaherty, F.: *New York State J. Med.* **17**:382, 1917 (two cases).  
 Geinitz, R.: *Beitr. z. klin. Chir.* **118**:252, 1920 (five cases).  
 Gillette, W. J.: *New York M. J.* **99**:1135, 1914.  
 Haggard, W. D.: *S. Clin. North America* **10**:719, 1930.  
 Holman, E.: Restoration of the Scalp, *J. A. M. A.* **84**:350 (Jan. 31) 1925.  
 Kirrison, M.: *Bull. et mém. Soc. de chir. de Paris* **38**:164, 1912.  
 Kopp, J.: *Cor.-Bl. f. schweiz. Aerzte* **41**:1206, 1911.  
 Lambret, O.: *Echo méd. du nord* **11**:416, 1907.  
 Landry, L. H.: *New Orleans M. & S. J.* **67**:782, 1914-1915.  
 Law, A. A.: *Surg., Gynec. & Obst.* **19**:229, 1914.  
 Lenormant, C.: *J. de chir.* **17**:9, 1921.  
 Luxembourg: *München. med. Wchnschr.* **60**:2759, 1913.  
 McWilliams, C. A.: Principles of the Four Types of Skin Grafting, *J. A. M. A.* **83**:183 (July 9) 1924.  
 Mallik, K. L. B.: *Indian M. Gaz.* **66**:86, 1931.  
 Meland, O. N.: *Minnesota Med.* **8**:116, 1925 (two cases).  
 Meyer-Burgdoff, H.: *Zentralbl. f. Chir.* **59**:1209, 1932.  
 Morrison, O. C.: *Internat. J. Med. & Surg.* **37**:493, 1924.  
 Moure, P.: *Bull. et mém. Soc. nat. de chir.* **53**:1040, 1927.  
 Muller, R.: *Beitr. z. klin. Chir.* **94**:10, 1914.  
 Northcutt, J. D.: *Kentucky M. J.* **23**:493, 1925.  
 Northrop, H. L.: *Hahneman. Monthly* **47**:666, 1912.  
 Nuzum, F. W.: Avulsion of the Scalp, *J. A. M. A.* **64**:1238 (April 10) 1915.  
 Painetvin: *Bull. et mém. Soc. de chir.* **38**:25, 1912.  
 Perthes: *München. med. Wchnschr.* **64**:1340, 1917.  
 Petridis, P.: *Bull. et mém. Soc. de chir. de Paris* **49**:1015, 1923.  
 Pond, E. M.: *M. Rec.* **44**:772, 1893.  
 Porter, C. A., and Sheddson, W. M.: *Boston M. & S. J.* **186**:727, 1922.  
 Rocher, H. L.: *Bull. et mém. Soc. de méd. et chir. de Bordeaux*, 1922, p. 58; 1923, p. 119.  
 Scott, R. G.: *Railway S. J.* **20**:54, 1913.  
 Shaw: *Tr. M. Soc. London* **46**:102, 1922-1923.  
 Snee, H.: *M. News* **62**:239, 1893.

- Stiles: Tr. Med.-Chir. Soc. Edinburgh **20**:50, 1900-1901.  
Viannay and Moreau: Ann. Soc. de méd. de Loire et la St. Étienne **38**:298, 1922.  
Weiss, T., and Hamant, A.: Rev. méd. d'est **49**:488, 1921.  
Wilisch, O.: München. med. Wchnschr. **58**:2330, 1911.

## CASES OF INCOMPLETE AVULSION

- Cayley, W.: Tr. Path. Soc. London **17**:440, 1866.  
Davis, J. S.: Johns Hopkins Hosp. Rep. **16**:257, 1911.  
Fairbank, F. R.: M. Times **41**:204, 1870.  
Gwyther: San Francisco M. Press **1**:179, 1860.  
Johnson, Z.: Dublin M. Press **29**:66, 1853.  
Lidell, J. A.: Am. J. M. Sc. **77**:305, 1879.  
Morone, G.: Clin. chir. **26**:918, 1919.  
Morton, T. G.: Philadelphia M. Times **11**:301, 1881.  
Robertson, F. M.: Lancet **2**:201, 1880.  
Scheinberg, G.: M. Rec. **90**:788, 1916.  
Schonbauer: Wien. klin. Wchnschr. **33**:180, 1920.

## GASTRIC SECRETION

### VI. THE ACTION OF PILOCARPINE ON THE SECRETIONS OF A TRANSPLANTED GASTRIC POUCH WITHOUT AUERBACH'S PLEXUS

EUGENE KLEIN, M.D.†

NEW YORK

Although there is no doubt that nervous stimuli excite gastric secretion, the precise source of the autonomic nerves which reach the secreting cells is as yet unknown. Two methods have been available for study: (1) histologic examination and (2) the use of drugs that stimulate and inhibit the sympathetic and parasympathetic systems. Utilizing transplanted subcutaneous gastric pouches previously described,<sup>1</sup> it seemed likely that these might yield results with the appropriate drugs. The pouches were constructed from the body and fundus of the stomach after stripping away the muscular coats together with the myenteric plexus and consisted of mucous membrane and submucosa. They were transplanted to the subcutaneous tissues of the abdominal wall with the blood supply at first intact. The blood vessels were severed at a subsequent operation. The result was a pouch deprived of vagus and sympathetic nerves and also of the myenteric plexus. Only the submucous plexus remained. Even the nerves accompanying the original gastric blood vessels no longer functioned, for the pouches were dependent on the abdominal wall for their new blood supply. The effect of atropine on such pouches has already been reported.

#### RELATIONS OF THE AUTONOMIC NERVOUS SYSTEM

The efferent pathways of both autonomic systems are believed to consist of two parts. In the case of the sympathetic system, the first neuron arises in the thoracolumbar segment and passes to one of the paravertebral ganglions or to one of the larger plexuses, such as the celiac plexus. From these ganglions the second or postganglionic neuron passes directly to the distal cells—the muscle cells in the circular or longitudinal coat of the stomach and intestine. The fibers, therefore (according to the present belief), pass directly through the myenteric and submucous plexuses. In the case of the parasympathetic system, the

---

† Dr. Klein died on Oct. 2, 1932.

From the Service of Dr. A. A. Berg and the Department of Laboratories, Mount Sinai Hospital.

1. Klein, Eugene, and Arnheim, Ernest: Gastric Secretion: I. A Transplanted Subcutaneous Gastric Pouch. *Arch. Surg.* 25:433 (Sept.) 1932.



first neuron arises in the bulbar (vagus) or sacral part of the spinal cord. It is supposed then to pass directly to ganglions situated in the walls of the peripheral structures, e. g., the myenteric plexus. From these ganglions the postganglionic fibers pass to the distal cells.

According to this theory the vagus nerve must communicate with its postganglionic neuron either in the myenteric or in the submucous plexus. The myenteric plexus consists chiefly of preganglionic vagus fibers. Its functions are incompletely understood, but it appears to be concerned with the normal muscular contractions (such as progressive peristalsis) of the stomach and intestine.

Little is known concerning the submucous plexus. It seems to have some relation to the muscularis mucosae. Any sympathetic fibers to this muscle or to the secreting cells may of course pass through it. But the nature of the cells in it and their relations to the vagus system, if any, are unknown.

Where the postganglionic vagus fibers to the secretory cells arise is also unknown. In the transplanted pouches used in these experiments, only the submucous plexus remained, so that the number of possible sites for the action of drugs became more limited.

#### ACTION OF PILOCARPINE

The present studies were performed with pilocarpine. This drug stimulates the parasympathetic system. It acts, according to Anderson,<sup>2</sup> on the neurocellular junction substance, just distal to the nerve endings. This observation was made on the muscles of the pupil of the eye. After degenerative section of the postganglionic fibers (short ciliary nerves) pilocarpine still caused contractions. Its action was counteracted by atropine. Admirable, however, as these experiments were, further corroboration in other organs seems necessary. Thus, Magnus<sup>3</sup> made some observations on strips of intestinal muscle peeled away from the myenteric plexus which show that pilocarpine increases their tone. This action too is inhibited by atropine. However, the usual marked contractions caused by pilocarpine do not occur in the absence of the myenteric plexus. Whether this is due to the fact that pilocarpine also acts on the plexus or that the removal of the plexus is in itself sufficient to prevent the normal contractions cannot be said.

While, therefore, Anderson's work seems to show that the site of maximum action is at the neurocellular junction, the possibility of some stimulation in the plexuses and the cells cannot be dismissed.

---

2. Anderson, quoted by Sollmann, Torald: *A Manual of Pharmacology*. ed. 3, Philadelphia, W. B. Saunders Company, 1926.

3. Magnus, quoted by Sollmann.<sup>2</sup>

As regards previous experiments, Suda studied the effect of pilocarpine in a Bickel pouch.<sup>4</sup> The latter is a gastric pouch entirely severed from the stomach, but retaining the original gastric blood supply. An attempt is made to section all the nerves visible in the mesentery. Though such a pouch is deprived of the major portion of its nerve supply, it cannot be stated definitely that all the sympathetic nerves in close relation to the blood vessels are severed. And it is also possible that some branches of the vagus nerve which pass through the semilunar ganglion and accompany the sympathetic nerves are missed. However, Suda found that the gastric cells in these pouches secreted acid on stimulation with pilocarpine. Because of the assumption that the branches of the vagus nerve pass directly to the secretory cells and that section of these branches to the pouch has been followed by degeneration of the nerve endings in the secretory cells, Bickel<sup>4</sup> concluded that the drug acts on the substance of the neurocellular junction. But his primary assumption is contrary to the conception now prevalent.

#### EXPERIMENTS

Tests with pilocarpine were performed on six dogs. Three had the type of transplanted pouch just described. One dog had the same type of transplanted pouch, but the original gastric blood vessels were left intact. Some sympathetic nerves may have reached the pouch along these vessels. The blood supply of this pouch was, however, much better than that of the pouches dependent on the abdominal wall, and the quantity of secretion was greater. This pouch, like the others, consisted only of mucous membrane and submucosa. The myenteric plexus was eliminated. Two dogs with ordinary Pavlov pouches were utilized for comparison.

The doses employed were 3.5, 5 and 7 mg. of pilocarpine hydrochloride. The drug was injected subcutaneously. The inhibitory effect of atropine on the action of pilocarpine was also studied. As in the results reported in previous papers, free hydrochloric acid, total acid and total chlorides are reported in the usual clinical units, that is, in cubic centimeters of decinormal solution. Pepsin is reported in units obtained by squaring the millimeter of Mett tubes digested and multiplying by 16; such results are, of course, not quantitatively accurate, but the relative observations are of some value. Frequently the amount of secretion was so small that determinations on the secretion of pepsin could not be made. In each table the secretion following the administration of 200 Gm. of meat and 250 cc. of water is given for comparative purposes. Altogether, forty-six tests were made. Tables 1 and 2 show the results with each type of pouch.

#### RESULTS

After doses of 3.5 and 5 mg. of pilocarpine hydrochloride injected subcutaneously, the appearance of free hydrochloric acid was inconstant. After doses of 7 mg. free hydrochloric acid always appeared

---

4. Bickel, Adolph: Ueber die Pathologie und Therapie der Sekretionsstörungen des Magens, Jena. Gustav Fischer, 1907.

(tables 1 and 2). This was true in all the pouches. Though pilocarpine was not as powerful a stimulant of free acid as histamine, in the larger doses fairly concentrated solutions were produced, the highest

TABLE 1.—*Effect of Pilocarpine Hydrochloride on Transplanted Denervated Gastric Pouch Without Myenteric Plexus*

Hour	Quantity of Juice, Cc.	Free Hydrochloric Acid	Total Acid	Pepsin*	Total Chlorides†
Test with Ment and Water					
1..... Fed 200 Gm. of ment and 250 cc. of water	1.2	0	25	16	...
2.....	0.7	5	50	..	...
3.....	0.3	10	50	81	...
4.....	0.55	30	70	..	...
5.....	0.82	30	75	..	...
6.....	0.64	15	60	64	...
Effect of 5 Mg. of Pilocarpine					
1..... 5 mg. of pilocarpine injected subcutaneously	0.6	0	30	..	...
2.....	1.4	0	60	64	...
3.....	1.3	0	50	100	...
4.....	0.7	0	40	81	...
5.....	0.55	0	60	..	...
6.....	0.60	0	50	..	...
Inhibitory Action of 1 Mg. of Atropine on Effect of 5 Mg. of Pilocarpine					
1..... 1 mg. of atropine injected subcutaneously; 5 mg. of pilocarpine injected fifteen minutes later	0.65	..	25	36	...
2.....	1.1	0	40	64	...
3.....	0.8	..	30	..	...
4.....	1.1	..	40	85	...
5.....	1.6	0	35	..	...
6.....	1.3	0	35	81	...
Effect of 7 Mg. of Pilocarpine					
1..... 7 mg. of pilocarpine injected subcutaneously	1.0	0	55	16	...
2.....	0.8	55	80	78	...
3.....	0.65	0	45	..	...
4.....	0.5	0	40	85	...
5.....	0.4	0	40	..	...
6.....	0.8	0	45	..	...
Inhibitory Action of 1 Mg. of Atropine on Effect of 7 Mg. of Pilocarpine					
1..... 1 mg. of atropine injected subcutaneously; 7 mg. of pilocarpine injected fifteen minutes later	1.4	0	10	..	144
2.....	0.6	0	15	..	144
3.....	0.55	0	15	..	...
4.....	0.4	0	15	..	...
5.....	0.5	0	10	..	148
6.....	0.2	0	10	..	...

\* Pepsin is expressed in Mett units.

† Total chlorides are expressed in cubic centimeters of tenth-normal solution.

free acid and total acid encountered being 60 and 115. This action persisted in the transplanted pouches for a period of one year.

After the smaller doses, when free hydrochloric acid was absent, an increase of secretion of pepsin occurred (table 1). The primary effect

apparently is the stimulation of secretion of pepsin and, in larger doses, of hydrochloric acid. This is in conformity with the results of Babkin's investigations.<sup>5</sup>

Owing to the small quantity of the secretion in the transplanted pouches, definite conclusions as to the effect of stimulation on the quan-

TABLE 2.—*Effect of Pilocarpine Hydrochloride on Subcutaneous Gastric Pouch Without Myenteric Plexus but with Original Gastric Blood Supply*

Hour	Quantity of Juice, Cc.	Free Hydrochloric Acid	Total Acid	Pepsin*	Total Chlorides†
Test with Meat and Water					
1..... Fed 200 Gm. of meat and 250 cc. of water	0.4	15	55	..	...
2.....	7.9	95	130	82	152
3.....	3.3	85	115	64	146
4.....	3.7	60	95	64	146
5.....	3.1	45	90	78	148
6.....	2.4	50	100	78	146
Effect of 5 Mg. of Pilocarpine					
1..... 5 mg. of pilocarpine injected subcutaneously	0.2	20	45	..	...
2.....	5.5	55	115	100	...
3.....	2.1	5	60	100	...
4.....	2.3	0	75	144	...
5.....	0.45	0	60	..	144
6.....	0.4	0	25	..	...
Effect of 7 Mg. of Pilocarpine					
1..... 7 mg. of pilocarpine injected subcutaneously	0.4	0	50	..	...
2.....	3.7	45	85	100	148
3.....	1.6	40	75	100	...
4.....	0.9	0	55	..	...
5.....	0.15	0	40	..	...
6.....	1 drop	0	..	..	...
Inhibitory Action of 1 Mg. of Atropine on Effect of 7 Mg. of Pilocarpine					
1..... 1 mg. of atropine injected subcutaneously; 7 mg. of pilocarpine injected subcutaneously fifteen minutes later	1.1	0	20	..	...
2.....	0.7	0	25	..	144
3.....	0.25	0	15	..	...
4.....	0.45	0	15	..	...
5.....	0.30	0	10	..	...
6.....	1 drop	0	..	..	...

\* Pepsin is expressed in Mett units.

† Total chlorides are expressed in cubic centimeters of tenth-normal solution.

tity cannot be drawn. Usually, but not invariably, when free acid was present the quantity was increased. In the transplanted pouch with the intact blood supply and in the Pavlov pouches, the quantity was always increased (tables 1 and 2).

One milligram of atropine always inhibited the secretion of free hydrochloric acid produced by 7 mg. of pilocarpine hydrochloride (tables

5. Babkin, B. P.: Die äussere Sekretion der Verdauungsdrüsen, Berlin, Julius Springer, 1928, p. 191.

1 and 2). The quantities of the secretion were also inhibited. When sufficient secretion for a test was obtained, though no free acid was demonstrated, secretion of pepsin persisted (tables 1 and 2).

#### CONCLUSIONS

It is evident that when allowance is made for the fact that the secretion in the transplanted pouches is much smaller than in the Pavlov pouches, the response in all the pouches to the stimulation of pilocarpine is similar. It is evident too that pilocarpine can stimulate the gastric cells to secrete pepsin and hydrochloric acid in the absence of both vagus and splanchnic nerves.

It is a striking fact that atropine inhibits the secretion of the hydrochloric acid but not of the pepsin produced by stimulation by pilocarpine. They are, of course, secreted by different cells. The variation may be due to the fact that the nature of the secretory process is different in each type of cell. The peptic cells build up "granules" which are then discharged, while the acid cells convert other chlorides to hydrochloric acid.

As the action of pilocarpine persists after the removal of the myenteric plexus, it is effective in the absence of postganglionic vagus fibers arising from the plexus. The possible sites of action that remain are: (1) possible nerve endings of fibers originating in the submucous plexus; (2) the neurocellular junctions, and (3) the cells.

The obvious next steps are the repetition of these experiments with physostigmine and choline.

It is important to emphasize once more that a parasympathicomimetic drug can stimulate gastric secretion in the absence of all extrinsic nerves and of the myenteric plexus. It is desirable to accumulate as many facts as possible tending to show such action in the complete absence of parasympathetic nerve supply. Should this be established it might permit the assumption of a working hypothesis that a stimulating substance may, under normal or pathologic conditions, exist in the peripheral circulation. The presence of such a stimulant would explain many obscure phenomena. In the sympathetic system such a known substance of course exists in epinephrine, which maintains its action after all the nerve supply has been eliminated.

#### SUMMARY

The site of origin of the postganglionic vagus fibers to the secretory cells is unknown. According to present theories, however, this should be either in the submucous or in the myenteric plexus.

Transplanted subcutaneous gastric pouches deprived of the vagus and sympathetic nerves and the myenteric plexus were used for this study. Control studies were done on Pavlov pouches.

Pilocarpine, a stimulant of the vagus system, was the first drug used. It is believed to act chiefly on the neurocellular junction.

Pilocarpine hydrochloride in doses of 3.5 and 5 mg. occasionally stimulates the secretion of free acid and at other times does not. Seven milligrams always stimulates such secretion. The secretion of fluids seems to run parallel to the secretion of acid. While the amount and the concentration of acid are not as high as after the injection of histamine, appreciable levels may be reached. The highest encountered in these experiments was 55 free acid and 115 total acid. This action has persisted for one year after the preparation of the pouch.

The smaller doses stimulated the secretion of pepsin even when no free hydrochloric acid appeared.

Atropine in doses of 1 mg. always inhibits the secretion of free hydrochloric acid and of fluid produced by full doses of pilocarpine hydrochloride (7 mg.). This is contrary to its effect on the action of histamine, which, with adequate doses, cannot be inhibited.

Atropine does not inhibit the secretion of pepsin produced by the injection of pilocarpine.

Pilocarpine remains effective after the vagus and the sympathetic nerves and Auerbach's plexus are eliminated. The exclusion of the plexus signifies the elimination of any postganglionic vagus fibers and their nerve endings which may originate there.

Experiments with choline and physostigmine, which act on nerve endings, should furnish further clarifying data.

# TREATMENT OF FRACTURES OF VERTEBRAL BODIES UNCOMPLICATED BY LESIONS OF THE CORD

WILLIAM A. ROGERS, M.D.

BOSTON

Recent fractures of vertebral bodies, uncomplicated by lesions of the cord, can be made to respond to treatment on the same general principles, and as satisfactorily, as major fractures of the large weight-bearing bones. Each of the latter presents distinct problems, owing to fundamental differences in structure and function. This is also true of the vertebral column, largely because of the peculiar structure and functions of the intervertebral disks, the frequent destruction of the disks as a result of injury and the high degree of adaptability of the column to such destruction under favorable treatment.

This thesis represents a study of the clinical course and early destiny of recent fractures of vertebral bodies without injury of the cord, the mechanics of their reduction by hyperextension and the mechanism of possible injury to the cord during reduction. It is based on a study of thirty-one consecutive<sup>1</sup> cases occurring in and near Boston between 1928 and 1932, inclusive.

## DIAGNOSIS

Early diagnosis is essential to satisfactory decompression, and accurate diagnosis, to safety in reduction and rational postreduction care. Failure to obtain decompression has occurred when there was a delay of more than seventeen days in making the diagnosis. Postponement of corrective treatment for four or five days or even a week does not seem to jeopardize the patient's chance of obtaining decompression, and occasionally seems wise because of shock, ileus or complicating injuries. But reductions after a week become, in the main, increasingly difficult as time passes. Furthermore, early diagnosis is important from the standpoint of the patient's morale. In a surprisingly large number of cases (13 per cent of the cases concerned here) recumbency was not insisted on by the surgeon in charge, under the impression that the patient had sustained a strain. Patients who are ambulatory immediately following fracture, with mild or no support, frequently experi-

---

This paper was presented as a thesis in application for membership in the American Orthopaedic Association.

This study, started in 1926, was made possible by an assignment of cases in the fracture service of the Massachusetts General Hospital.

1. Two cases in which the patients were treated by former methods cannot be traced and are not included.

ence severe incapacitating pain, and thereby come to regard their injury in a light far more disquieting than it deserves when its true nature is finally disclosed. Commonly, the layman believes that fracture of the spine means crippleddom, paralysis or death. If the person with an injured spine were rendered comfortable from the start, especially in industrial and automobile accidents, much of this misapprehension could be allayed and better cooperation obtained.

Both from the standpoint of the patient's safety from injury to the cord during reduction and from that of loss of correction during recovery, accurate diagnosis must be obtained. This is possible only through roentgenograms revealing the best obtainable bone detail in anteroposterior and lateral planes. The roentgenograms should include the entire vertebral column, since scattered fractures may be present, some of them silent. The roentgen study should also include the lumbosacral junction for local factors predisposing to subsequent strains, since this region suffers most through failure of correction.

Injury of the spinal cord is in most cases the result of dislocation, either momentary or fixed. Therefore, if dislocation is present, or there is evidence that momentary dislocation occurred at the time of injury, it becomes apparent that the safety of the cord in that case is diminished, and the utmost caution is necessary in effecting reduction or, indeed, proceeding with any policy of treatment.

Patients not showing paralysis but revealing mild symptoms of injury of the cord in the form of reflex changes, bladder retention, paralysis, variations in muscle tone or hyperpyrexia possess a low factor of cord safety. These points should be carefully determined before proceeding with reduction rather than after disaster.

In arriving at an accurate roentgenologic diagnosis,<sup>2</sup> the following points should be carefully noted:

1. (a) Loss of the concavity of the anterior surface of the vertebral body; (b) zone of increased density; (c) intestinal gas patterns suggesting ileus
2. Lateral and anterior wedging
3. Fragmentation and saucerization of the articular surfaces
4. (a) Narrowing of the adjacent intervertebral spaces; (b) narrowing of the other intervertebral spaces
5. The condition of the posterior bony structures, i. e., the spinous and articular processes, the laminae and pedicles
6. Crushing of the posterior wall of the body
7. Anterior and lateral dislocation of one body on another
8. Spurring (proliferative changes)
9. Defects in the lumbosacral region

---

2. Dr. William Martin of the department of radiology, Massachusetts General Hospital, painstakingly reviewed all the roentgenograms in this series.



Points 1*a* and 1*b* were present in all the cases and seemed diagnostic; point 1*c* was frequent in very recent cases; point 2 gives an estimate of the derangement of the mechanics of the back and is important from the standpoint of fixation; points 3 and 4 indicate the degree of disorganization of the intervertebral disk; points 5, 6 and 7 give an estimate of the factor of cord safety from the standpoint of reduction, and points 8 and 9 are important in prognosis and indicate a back already predisposed to strain.

Complicating injuries must not be overlooked. Not uncommonly, the os calcis, the sacro-iliac joints, the transverse processes, the ribs and the sternum share with the vertebral body the effect of the trauma.

#### ETIOLOGY

The usual injuries causing fractures of vertebral bodies and their importance in diagnosis have been frequently and well described in the literature. Attention has often been called to the common error among surgeons of failing to recognize the condition early.

#### EARLY DIFFICULTIES IN CORRECTING VERTEBRAL INJURIES

Correction of a deformity resulting from compression of a vertebral body was first demonstrated by Dr. Arthur G. Davis of Erie, Pa., in 1924. He fully described his technic in 1929.<sup>3</sup> Prior to the publication of Davis' work, Dunlop of Pasadena, Calif., and I at the Massachusetts General Hospital, working independently, were consistently obtaining corrections—likewise by extension but by widely different technics. Complete hyperextension of the vertebral column is the keynote of reduction by whatever method is employed. Earlier attempts to reduce such fractures were made, some of them forcible, but none was apparently demonstrated to be successful and none of the methods was consistently practiced. The fear of injuring the cord during reduction seems to have been the reason for the failure to carry extension far enough to be successful.

Reports of other methods of reduction rapidly appeared in the literature<sup>4</sup> following the publication of Dr. Davis' article. Full descriptions of these technics, each yielding satisfactory reductions, are given in these articles.

3. Davis, A. G.: *J. Bone & Joint Surg.* **11**:133 (Jan.) 1929.

4. (a) Dunlop, J., and Parker, C. H.: *Correction of Compound Fractures of Vertebrae*, *J. A. M. A.* **94**:89 (Jan. 11) 1930. (b) Rogers, W. A.: *Surg., Gynec. & Obst.* **50**:101 (Jan.) 1930. (c) Jones, R. W.: *Brit. M. J.* **1**:300 (Feb. 2) 1931. (d) Dunlop, J., and Parker, C. H.: *Radiology* **17**:228 (Aug.) 1931. (e) Dunlop, J., and Parker, C. H.: *J. Bone & Joint Surg.* **15**:153 (Jan.) 1933.

The results of treatment in cases of unreduced fracture often leave much to be desired. Studies of the end-results by a number of authors indicate a long period of disability in a high percentage of cases. The cause of disability is usually backache due to muscle strain, not at the site of fracture but along the course or at the attachments of the erectors spinae. Frequently recurring strains are common during the first two years. This is occasioned by the exaggeration of the anteroposterior spinal curves incident to the deformity of a vertebra, and the difficulty which the muscles experience in accommodating themselves to this change. Treatment by postural exercises and support, granted cooperation by the patient, has proved successful, but often at the cost of two years' disability. Spinal fusion has also been tried extensively in uncorrected cases. Fusion in such cases eliminates pain at the site of fracture and in the corresponding peripheral nerve segments (in my experience, very infrequent complaints), but it does not eliminate muscle strain and does not relieve the vertebral column of the decided mechanical disadvantage under which it is placed by the deformity of the vertebra and the common loss of one of its intervertebral disks.

#### MECHANICS OF REDUCTION

Any analysis of the mechanics of the normal vertebral column must be based at present on the anatomic researches of Schmorl and his co-workers in Dresden, where seven thousand spines obtained at necropsies in the years from 1925 to 1930 have been carefully scrutinized.<sup>5</sup> This extensive material, exhaustively studied, has led to the best scientific description to date of the normal and pathologic anatomy of the vertebral column. This structure may be likened to a flexible segmented rod (Lovett) of great strength, capable of a remarkable degree of adaptation to torsion, tension and pressure and of resistance to mechanical shock and "wear and tear." These properties are possible because of the intervertebral disks, which are essentially highly specialized articulations between the vertebral bodies, and which comprise almost a quarter of the length of the column (Weber). The further functions of protection to the spinal cord, of affording muscle attachments and of posterior reinforcement are provided by the posterior bony structures. The intervertebral disks differ from other articulations in that the tissue of the nucleus pulposus is present, instead of a joint cavity. Whether the nucleus is a fluid confined under pressure within an elastic container, the annulus fibrosus, as suggested by Keyes and Compere,<sup>6</sup> or whether

5. Beadle, O. A.: *The Intervertebral Discs*, London, His Majesty's Stationery Office, 1931.

6. Keyes, D. C., and Compere, E. L.: *J. Bone & Joint Surg.* 14:897 (Oct.) 1932.

it possesses an inherent turgor which is held in check by the elastic fibers of the annulus and the pressure of the vertebral bodies on the intact cartilaginous end-plates, as suggested by Schmorl, the experience of the last five years has convinced me that it must act as the means of contact and hence as the fulcrum between vertebrae. Since the nucleus is not definitely demarcated, and its shape and relative position are altered somewhat with each change in the position of its contiguous vertebrae,

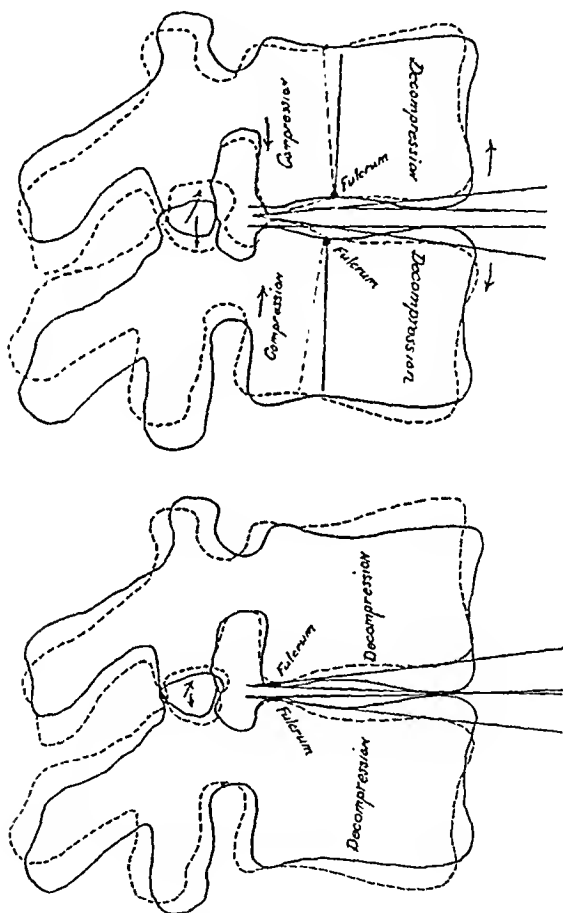


Fig. 1.—Diagram showing mechanics of spinal column: Upper illustration, normal; lower illustration, abnormal as in fracture of vertebra.

this point of contact must shift somewhat with each change in position of the vertebrae. For this reason, it does not seem possible to postulate precisely any single axis of motion between vertebrae. But it may be stated that the axes of motion lie along a line drawn through the point where the greatest resistive pressure of each intervertebral disk falls on its contiguous vertebrae. For all practical purposes, this line falls through the nuclei pulposi (fig. 1 upper part), near the deepest point of concavity of the articular surface of the centrum. Thus, any

force applied to the vertebral column to extend it exerts a decompression or tension throughout those portions of the vertebrae anterior to the line of the nuclei pulposi, and a pressure along those portions of the vertebrae posterior to that line. Along the line there is neither compression nor decompression, and it may be referred to as the neutral line. This may be easily demonstrated by lateral roentgenograms of the lumbar region of a normal person in extreme flexion and hyperextension. The axis of motion of each vertebra may be seen to fall through the concavity opposite the nucleus. It is because of the decompression which occurs in extension that fractures of the vertebrae can be reduced. It may be noted in the roentgenograms in cases in which the disk is not appreciably altered that the vertebra fractured through its superior or inferior surface at or in close proximity to the nucleus pulposus show at that point little or no correction following extension, whereas anteriorly, in the zone of decompression, the centrum may be restored virtually to its prefracture dimensions. Another fractured well posterior or well anterior to the nucleus may be decompressed to such a degree as to represent almost complete anatomic restitution. This consistent finding is interpreted as the result of either a feeble decompression or absence of it in the region of the nucleus, or as the result of a positive pressure from that portion of the disk made up largely of nuclear material.

It was demonstrated by Schmorl's work, and confirmed in the present series, that in injuries resulting in compression fracture the nucleus pulposus is frequently not spared (figs. 2 and 3). It may suffer complete disorganization in severe cases; in others, moderate alteration in which some of its functions may for a time, at least be preserved, or, in some mild compressions, little or no disorganization of either structure or function.

Although the condition of the disk may only be inferred from the roentgenogram, I have divided the cases into four groups for the purpose of analysis of (1) the mechanism of extension and (2) the treatment.

Group 1 includes fractures in which destruction of the disk is slight or absent. Absence of narrowing of the intervertebral space and of evidence of more than minor fragmentation of the articular surface seems to indicate that the disk is functioning. The mechanics of extension is virtually that of the normal (fig. 1, upper part). Eight, or 26 per cent of the cases in this series, fell in this group. Excellent reductions were obtained in all (case 1, fig. 4).

Group 2 includes fractures in which the superior or the inferior surface of the centrum and the adjacent intervertebral disk are extensively disorganized. Here it immediately becomes apparent that the inevitable destruction of the nucleus pulposus has deprived the vertebrae of their normal contact and hence normal axis of motion. Extension

occurs through an axis well posterior to the normal—roughly, at the posterior wall of the centrum (fig. 1, lower part). The arc of motion of the laminae and articular processes is short and falls well back of the spinal cord, and the possibility of injury to the cord in extension is almost prohibitive, through the limitation of the longitudinal ligament anteriorly and of the contact and locking of these structures posteriorly. Sixteen cases, or 51 per cent of the series, fell within this group, in all of which corrections were good (case 10, fig. 5; case 12, fig. 6).

Group 3 differs from group 2 only in the deformity of the vertebral body: the compression is essentially central rather than anterior or lateral. The walls of the centrum are but slightly compressed. The

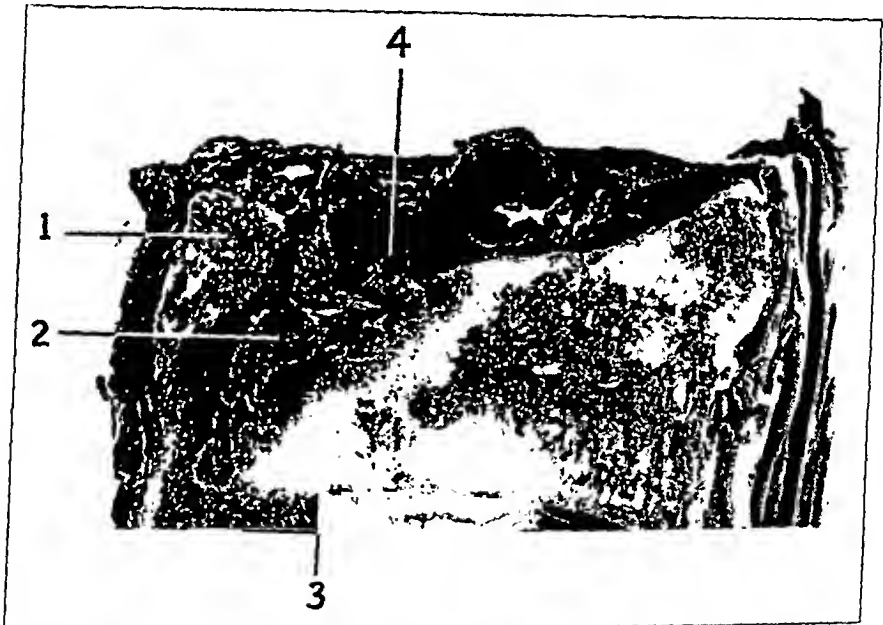


Fig. 2.—Gross photograph of the third lumbar vertebra seven weeks after partial correction. Death occurred from hemorrhage of a gastric ulcer. The vertebra shows: (1) anterosuperior bone fragment; (2) fracture line (fig. 3); (3) hemorrhagic areas and compressed spongiosa, and (4) disorganized intervertebral disk pressed into the space between the fragments.

The sections shown in this figure and in figure 3 and the interpretations thereof were made by Dr. Sidney Farber, Department of Pathology, Harvard Medical School.

articular surface is saucer-shaped. Little or no decompression can be obtained by extension. The intervertebral space may be restored. Two cases, or 6 per cent of the series, comprised this group (fig. 7, case 25).

Group 4 includes cases of compression fracture with dislocation of the above adjacent vertebra. The nucleus pulposus has, through the injury, lost its mechanical identity. If during extension posterior replacement of the dislocated vertebra does not occur, the axis of motion falls

through the new point of contact between these vertebrae, namely, near the posterior wall of the displaced vertebra and forward on the superior surface of the fractured vertebra. The arc of motion of the laminae and articular processes of the dislocated vertebra in extension is such that with each increment of extension, these elements encroach farther on the spinal canal until they lock. If, however, the posterior bony proc-



Fig. 3.—Photomicrograph of a section of the specimen shown in figure 2 ( $\times 10$ ; aniline blue stain) taken to include a portion of the anterosuperior fragment, the fracture line and the main fragment. The fracture line contains annular fibers and nuclear material disorganized by the injury and pressed into the fracture mass. The picture shows: (1) anterosuperior bone fragment, (2) fracture line and (3) main fragment.

esses do not lock (always a possibility in fracture of the articular process) injury of the cord ultimately ensues (figs. 8 and 9). Five cases, or 16 per cent of the series, fell in this group.

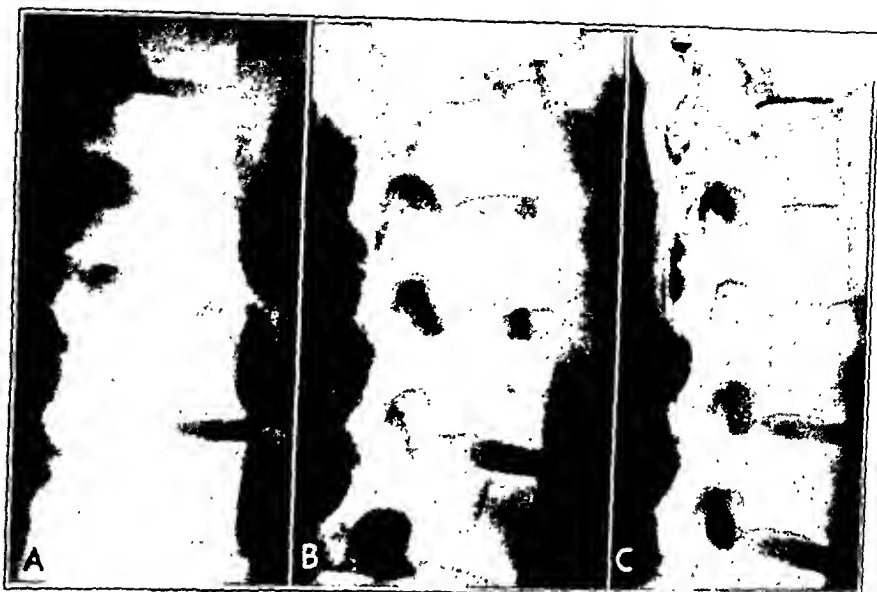


Fig. 4.—Roentgenograms illustrating injury of vertebra and result of treatment typical of group 1 (case 1). In this case there was no apparent fracture or narrowing of the intervertebral disk. Treatment was by flexible frame, for reduction, and fixation by recumbency in a plaster of paris jacket, ambulatory treatment in a plaster jacket and finally a high backbrace. *A* shows appearance before reduction; *B*, appearance after reduction, during ambulatory treatment in the plaster jacket, and *C*, end-result three years and five months after injury.



Fig. 5.—Roentgenograms illustrating group 2 (case 10). In this case there was fracture of the superior vertebral surface with no definite narrowing of the intervertebral disk. Treatment was by flexible frame, for reduction, and fixation in shells, followed by fusion and recumbency in a plaster jacket, then by ambulatory jacket treatment and finally a high backbrace. *A* shows appearance before reduction; *B*, appearance after reduction, and *C*, end-result after four years.



Fig. 6.—Roentgenograms illustrating group 2 (case 12). In this case there was fracture of the superior vertebral surface with narrowing of the intervertebral disk. Treatment was reduction by flexible frame and fixation by shells, followed by ambulatory treatment in a plaster jacket and last a high backbrace. *A* shows appearance before reduction; *B*, appearance after reduction, and *C*, the end-result after four years.

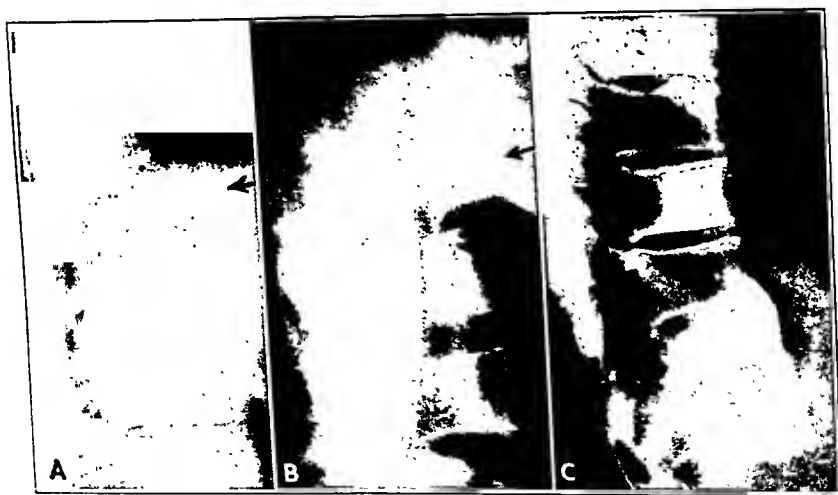


Fig. 7.—Roentgenograms illustrating group 3 (case 25). In this case there were fractures of both surfaces of the vertebra with narrowing of the intervertebral disk. Treatment was reduction by flexible frame and fixation by recumbency in a plaster jacket, followed by ambulatory treatment in a jacket and finally a high backbrace. *A* shows appearance before reduction; *B*, appearance after reduction, and *C*, the end-result after two years and five months.



In one case in this group (case 28) manifestations of impending injury of the cord developed during extension; in another (case 30), so much pain that extension was stopped, apparently just short of injury to the cord, as shown at operation. Posterior replacement of the dislocated vertebrae was obtained in two cases.

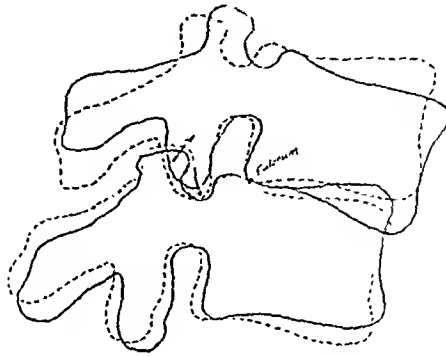


Fig. 8.—Diagram showing mechanics of extension in group 4.

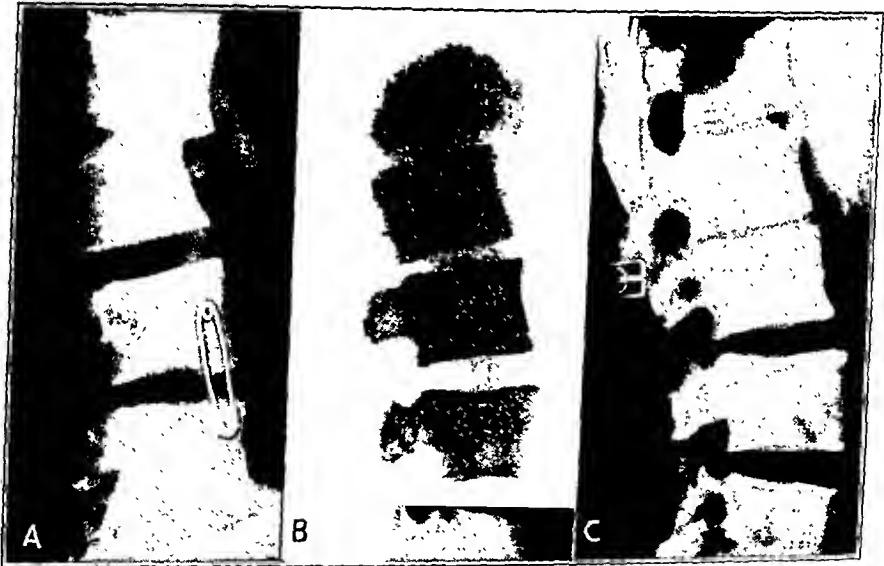


Fig. 9.—Roentgenograms illustrating group 4 (case 27). In this case there were noted: wedging of the vertebral body (anterosuperior lip of second lumbar vertebra), apparent fracture of the anterosuperior lip of this vertebra, obliteration of the intervertebral space, and dislocation of the anterior parts of the first and second lumbar vertebrae. Treatment was reduction by Bradford frames and fixation by shells for three months, spinal fusion, and wearing of a high backbrace. *A* shows appearance before reduction; *B*, appearance after reduction, and *C*, the end-result after four and a half years.

Mention should also be made of the anterior longitudinal ligament which is, as stressed by Davis, so powerful, its tenacity to the vertebral bodies and the disk so great, and its continuity during life so indestructible that it should be mentioned as decidedly a factor in reductions through extension. This ligament limits hyperextension, and with the annulus fibrosus provides the agency through which the forces of decompression operate.

It seems probable that the influences of decompression do not exert their full effect on the fractured vertebrae until complete hyperextension of the intervertebral joints above and below the fracture has been reached, since force applied up to that point is spent in physiologic extension of joints above and below. Clinical experience seems to bear this out. Numerous failures to decompress occurred in cases in which extension was carried out only partially.

#### APPARATUS AND TECHNIC OF DECOMPRESSION

The apparatus employed in obtaining complete hyperextension in the method of treatment discussed here was described <sup>4b</sup> in 1930 and has remained essentially unchanged since, except that it has been simplified and so arranged that roentgenograms can be obtained at the time of reduction, and plaster fixation applied without moving the patient from the frame. The essential principle of placing the patient supine on a flexible Bradford frame and obtaining extension by rendering the frame convex upward is the same. The flexible frame, in its segment which underlies the vertebral column in extension, assumes virtually the normal extension curve, except in the upper dorsal region where a thickening of the mattress of blankets employed evens the pressure. The force is very great and is under absolute control. It may be applied so gradually that increments of extension are scarcely appreciable by the patient. The corrective force is that of gravity under absolute control through the frame, and is the resultant of traction and extension. Traction may be augmented by weight and pulley or manually by assistants. Figures 10 to 13 show the structure of the frame.<sup>7</sup> It may be seen that by slowly lowering the ends of the frame the spine is gradually extended. Note the extreme upward convexity necessary to provide complete hyperextension. Formerly the yoke, intermediate between the ends of the flexible frame and over which the frame is bent, was placed opposite the kyphos. This did not always yield an extension free from discomfort to the patient. It is now placed in the region of the dorso-lumbar junction so that physiologic extension of the spine may be obtained without pain.

When the apparatus is being set up, the yoke can be adjusted to the flexible frame on which the patient lies during extension, at the point where the dorso-lumbar junction will rest.

7. Dimensions: height, 5 feet and 2 inches (157.5 cm.); length, 5 feet and 10 inches (177.8 cm.); width, 3 feet (91.5 cm.); height of yoke, 3 feet and 1 inch (94 cm.); seamless steel tubing,  $\frac{1}{2}$  inch, 1.27 cm. (top bar, 1 inch [2.5 cm.]); length of flexible frame, 7 feet (213.3 cm.); width of flexible frame, from 18 inches to 24 inches (45.7 to 60.9 cm.); spring steel bands,  $\frac{3}{16}$  inch by  $1\frac{1}{4}$  inches (0.48 by 3.18 cm.).

The width of the flexible frame can be varied so that for any patient the side bands will be at a distance of about 3 inches (7.6 cm.) from the torso. This makes it possible for the roentgenologist to place the tube and cassette at the desired distances to obtain checkup roentgenograms. Furthermore, with 3 inch

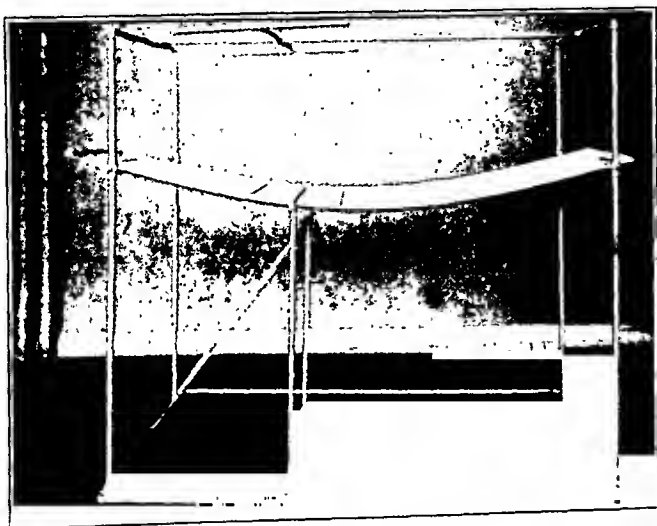


Fig. 10.—The flexible Bradford frame.

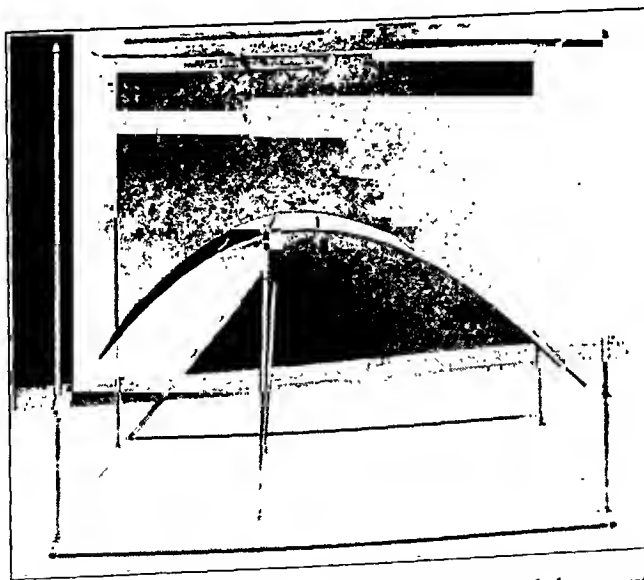


Fig. 11.—The flexible frame arranged as for spinal hyperextension.

spaces on each side of the torso, the side bands do not interfere with the application of a plaster jacket.

When it is planned to use a plaster jacket following the reduction (fig. 14), a piece of webbing about 4 inches (10 cm.) square is placed on the matted frame where the lumbar region will rest when the patient is placed on it. To the two sides of this piece have been sewed six 1 inch (2.5 cm.) webbing

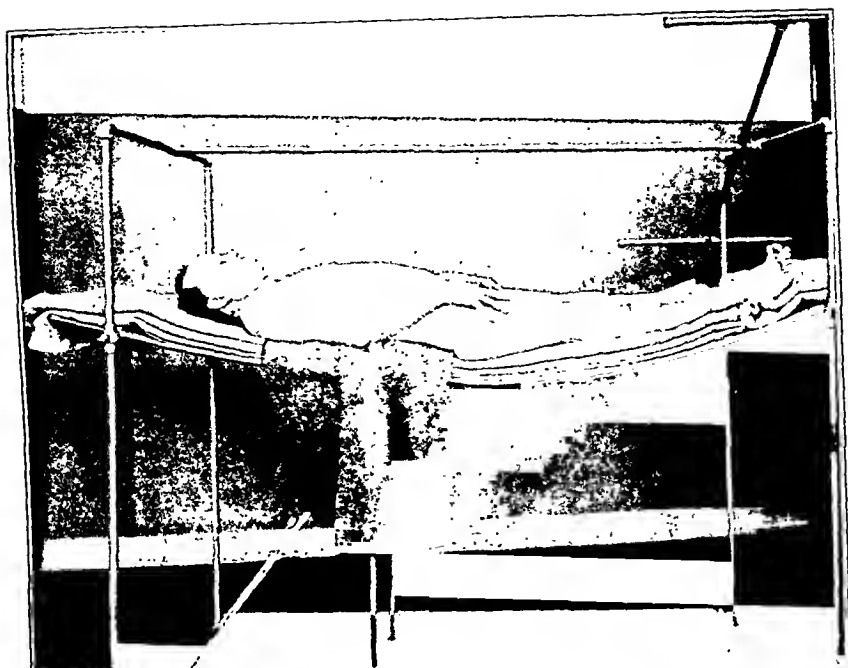


Fig. 12.—The patient properly placed on the flexible frame, yoke at the dorso-lumbar junction, and a mattress of blankets arranged, with webbing in place.

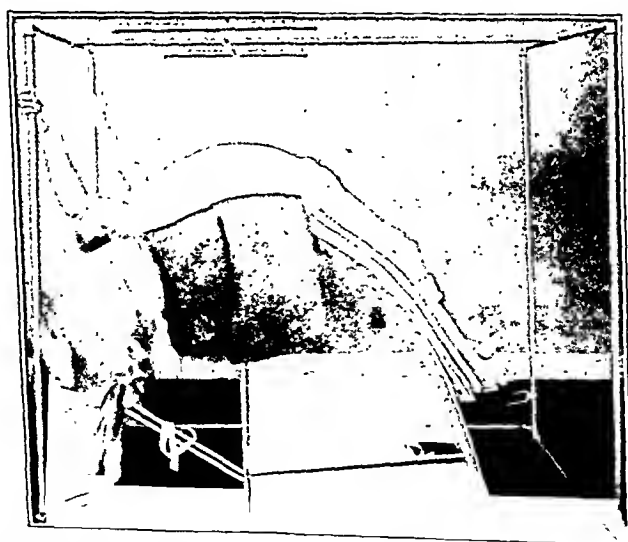


Fig. 13.—Note the extreme upward convexity necessary to provide complete hyperextension.

straps about 1 foot (33 cm.) long, three on a side, and each equipped with a buckle. The four straps at the corners of the square are sewed obliquely; the two at the middle, at right angles to the sides. Over this is placed the felt padding for the jacket, and the patient is then laid on the frame. As quickly as hyperextension has been obtained, these six straps are fixed through buckles to corresponding straps fastened to the adjustable overhead piece and tightened. The segment of the canvas covering of the frame underlying the vertebral column from the middorsal to the midsacral region is now removed from beneath. The patient's torso is thus made easily accessible for the application of the jacket while it is still maintained in hyperextension.

The technic of reduction has been radically changed since it was first described<sup>4b</sup> in 1930. Extension was then carried out slowly, so that the first correction in July 1928 was found by roentgenogram after fourteen days of gradual

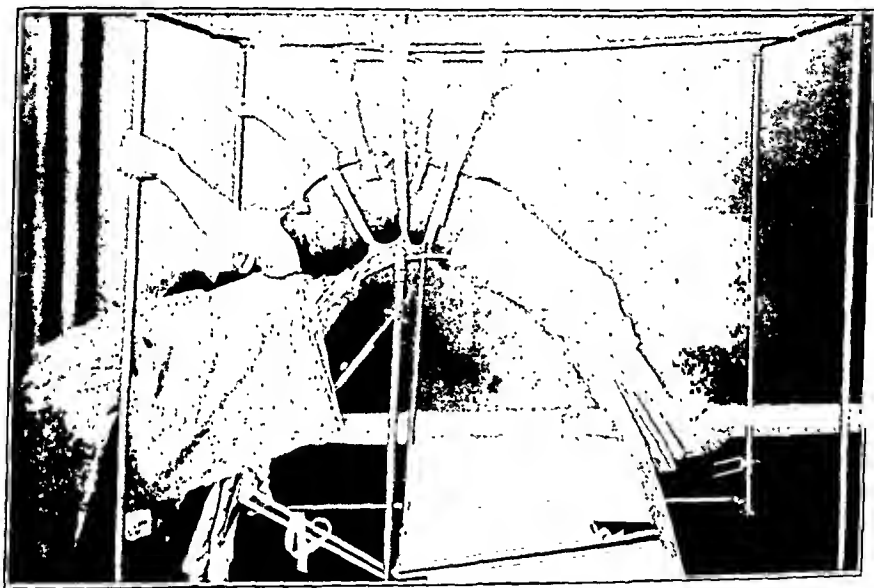


Fig. 14.—The application of a plaster jacket requires that the patient be suspended while still in extension.

extension. The rate of extension after this case was accelerated to reduce the time of correction to from four to seven days. The reason for such slow extension was that injury to the cord might surely be avoided, as such impending injury would be manifest before the damage was done. With better appreciation of the mechanics of correction and of the type of case which seems to have a low factor of cord safety the time of correction has been cut down during the past eighteen months to a few minutes (from fifteen to sixty) with as satisfactory restoration as before, apparently fully as much safety and less inconvenience to the patient. There is one exception to this practice which should be definitely understood, namely, its employment in cases which fall in the fracture-dislocation group. In this group, which might be termed, from the standpoint of injury to the cord, the "potentially dangerous group," further study will be necessary before any procedure may be advocated.

General anesthesia was not necessary in the cases in this series, nor was the employment of any local anesthesia indicated. An average dose of morphine-

scopolamine, appropriate to the patient's age and weight, may be given to allay apprehension, and also to promote relaxation of the muscles, but not to render the patient insensible to questioning or to pain more definite than discomfort. This medication has proved helpful and is recommended. The canvas-covered flexible frame on which the patient lies supine is heavily matted with blankets. Extension is started with the frame concave upward, and only after the adjustment of the frame is such that the patient is comfortable. The lower extremities are exposed in order that reflexes may be checked from time to time, voluntary muscle action carefully watched for early paralysis, and any other manifestation of injury to the cord noted. Reflexes tested too frequently tend to fatigue, and during the latter range of extension there has been uniformly a diminution in the intensity of response in the knee jerks.

It is practically essential to the patient's comfort and cooperation that the head be kept horizontal and not dependent. To this end, head pillows are provided as extension is increased. This provides comfort without hindering extension, since the highly flexible cervical spine does not appreciably influence the dorsal and lumbar segments.

Extension is slowly and intermittently increased in small increments until the surgeon estimates that the limit of hyperextension has been reached. This limit varies widely with age, habitual posture, type and proliferative changes, all of which should be considered. A general estimate may be reached by determining the angle between two imaginary planes on the anterior aspect of the fully extended torso: the first, the mean plane of the sternum; the second, a plane passing tangent to the anterior superior spines and the two anterior-most points of the lower thoracic margins. This angle varies roughly between 45 and 60 degrees, the former in the stocky, heavy-boned type, the latter in the long, slender-boned, hypermobile type. Usually at the stage where this angle falls within these limits the patient experiences a strong limiting pull of the rectus abdominis and anterior hip muscles, and after a little more extension lumbosacral pain begins, rapidly increasing in intensity with further efforts at extension. The latter subjective manifestations are not in themselves reliable, since it is a common experience to encounter them some time before complete extension is reached, only to have them no longer felt at that degree of extension after a few minutes at a less advanced degree. When they invariably appear at the same degree of extension, obviously near the limit, at a second or third trial at further extension, the limit has probably been reached. This process of gradually obtaining the full range through intermittent applications of extending force usually takes from twenty to thirty minutes. Lateral roentgenograms may then be made with a portable unit and the wet films interpreted. The appropriate fixation is then applied while the patient is still on the frame. When this has hardened, the patient is returned to bed. The whole procedure consumes about one and one half hours.

#### EXPLANATORY NOTE

The reductions obtained in this series, the experiences with fixation, the roentgenographic changes noted and the end-results to date are recorded in the tables. It is hoped that in this way a fair cross-section of the experience on which the study is based will be presented. Reproductions of all the films would require so much space, and important detail in the originals would be so often lost, that the tabulation method

seems to be the only practical way of disclosing the results and correlating the findings. The reproductions shown have been selected to emphasize high points, which it is meant thereby to stress. Each print discloses one or more points discussed, and by comparing what is to be seen in it with the corresponding note in the tables the reader will be able to gage the actual experience with the series.

#### RESULTS IN THIRTY-ONE REDUCTIONS (TABLE I)

Roentgenograms taken following reduction in the twenty-four cases in groups 1 and 2 show almost complete correction in the matter of the shape of the body with three exceptions (cases 9, 18 and 21). In all, there remained a slight but definite deformity, in some almost imperceptible, in others more quickly recognizable. In all except one the impression could be gained that the vertebral body was diminished in size. In case 9 (July 1928) it was decided to attempt no correction of the bone but simply to carry out exercise and supportive measures, i. e., as a control. In case 18 (January 1931) extension was stopped short of completion because of the recurrence of an old strain in the lower part of the back which proved painful and apparently was caused by the extreme position. In this case, correction fell short of the foregoing standard. In case 21 (February 1932), through an error in hospital routine, roentgenograms were not taken the day following reduction, and on the fourth day while straining at stool the patient suffered a pulmonary embolus which almost proved fatal, and which required the removal of the jacket after the acute phase had passed.

In all cases of groups 1 and 2, with the same exceptions, no definite narrowing of the intervertebral space could be detected directly after reduction.

The fractures in group 3, the central compression type, could not be decompressed. The disk fibers, it seemed, were so disorganized as to make little if any effective traction possible. Only two such cases appeared in the series, and this experience may therefore prove not to be the rule. In case 26, the intervertebral space was restored twelve weeks after its obliteration, a common experience in the old, uncorrected cases.

The fractures in group 4, five in number, did not give consistently good results. Only two were reduced fully (cases 27 and 31). The patient in case 30 came for reduction twenty-three days after injury—apparently too late for the fracture to yield, although some correction was obtained. The patient in case 28 showed during correction temporary interruption of cord function before complete hyperextension could be obtained. The failure of correction in case 28 (March 1929), in which a four day correction was attempted, cannot be definitely explained. The patient was not cooperative.

*Lapse of Time Before Patients Came for Reduction.*—Reductions started within seventeen days after the date of injury were uniformly successful, and those started after seventeen days were either partially or entirely unsuccessful. The optimum time for reduction, however, is clearly during the first week.

*Age of Patients (Table 3).*—The youngest patient was 15 years of age. Four were in the third decade, ten in the fourth and six in the fifth. One was 63 years of age and the oldest was 64.

*Apparatus Employed in Reductions.*—In all cases except two the flexible frame was used to effect reductions. In case 2, the patient was simply hyperextended by placing him on the Goldthwaite irons. In case 27, the fracture was reduced by using two Bradford frames, shifting the patient back and forth from one to the other for more than fourteen days, the frames being bent farther each time.

*Time of Reduction.*—During the period of gradual correction, from June 1928 to June 1931, the average time of correction was seven days. Since then, the average time of correction has been about twenty minutes. Twenty of the patients were extended gradually, and ten in less than one-half hour.

*Gross Appearance of Fractures.*—In table 1, under the heading "Gross Appearance of Fracture, or Fracture and Dislocation," the degree of anterior wedging is estimated in terms of the approximate loss in height of the anterior surface of the vertebral body through compression. None of the patients showed beyond question compression of the posterior wall of the centrum. In only two was there lacking some evidence of fracture of one or both of the articular surfaces of the centra (cases 1 and 4), and in only two others was this indeterminate.

The term "saucerization," coined to describe the articular surface in fractures which by roentgenogram are essentially central compressions, is not applied outside group 3 in the table. Many of the other fractures showed some central compression, however, but not sufficient to make this element predominant over wedging.

Twelve patients showed no definite narrowing of the intervertebral space, either superior or inferior. In all others, the violence had unquestionably narrowed the space.

For details concerning fracture definitely demonstrable in the posterior bony processes, see table 4, under "Complications."

*Cord Injury Through Reduction.*—All the patients were carefully watched during correction for evidence of impending injury to the cord, especially weakness in voluntary muscle action in the lower extremities, loss of reflexes or twitching. None received local or general anesthesia. In only one case was there evidence even of interruption of cord function. Two patients (cases 28 and 30), however, gave reasons for



TABLE 1.—Summary of Experience in Thirty-One Reductions

Group and Case	Date	Lapse of Time Before Patient Came for Reduction, Days	Apparatus Used	Time of Reduction	Vertebrae Involved	Gross Appearance of Fracture, or of Fracture and Dislocation (Group 1)			Correction	
						Estimated Wedging of Body	Apparent Fracture of Articular Surface	Inter-vertebral Space	Shape of Body	Inter-vertebral Space
Group 1:										
1	9/17/29	13	Flexible frame	10 days	L-1	Loss of about $\frac{1}{2}$ (anterior)	None	No definite narrowing	Almost complete	No definite narrowing
2	4/ 8/30	10	Goldthwaite irons	Few min.	L-2	Loss of about $\frac{1}{4}$ (anterior)	Superior	No definite narrowing	Almost complete	No definite narrowing
3	12/18/30	1	Flexible frame	3 days	D-8	Loss very slight (anterior)	Superior	No definite narrowing	Almost complete	No definite narrowing
4	3/30/31	17	Flexible frame	6 days	L-1, 2, 3 and 4	Anterosuperior lip of each	L-1 None L-2 Superior L-3 Superior L-4 Superior	No definite narrowing	Almost complete	No definite narrowing
5	7/23/31	0	Flexible frame	About 20 min.	L-1	Loss of about $\frac{1}{2}$ (lateral and anterior)	Superior	No definite narrowing	Almost complete	No definite narrowing
6	10/ 4/31	3	Flexible frame	About 20 min.	D-12	Loss of about $\frac{1}{2}$ (anterior)	Questionable	No definite narrowing	Almost complete	No definite narrowing
7	11/12/31	14	Flexible frame	About 20 min.	D-12	Loss of about $\frac{1}{2}$ (anterior)	Superior	No definite narrowing	Almost complete	No definite narrowing
8	11/21/31	11	Flexible frame	About 20 min.	L-2	Loss of about $\frac{1}{4}$ (anterior)	Superior	No definite narrowing	Almost complete	No definite narrowing
Group 2:										
9	7/28/28	No correction	.....	.....	L-3 and 4	L-3, none L-4, loss of about $\frac{1}{4}$ (anterior)	Both superior	Narrowed	None	None
10	9/29/28	2	Flexible frame	4 days	L-1	Loss of about $\frac{1}{2}$ (anterior)	Superior	No definite narrowing	Almost complete	No definite narrowing
11	1/23/29	3	Flexible frame	8 days	D-12	Loss of about $\frac{1}{4}$ (anterior)	Indeterminate	Narrowing	Almost complete	No definite narrowing
12	3/ 4/29	10	Flexible frame	9 days	D-12	Loss of about $\frac{1}{2}$ (anterior and lateral)	Superior	Narrowing	Almost complete	No definite narrowing
13	3/ 9/29	9	Flexible frame	11 days	D-11	Loss of about $\frac{1}{4}$ (anterior)	Both	Narrowing	Almost complete	No definite narrowing
14	11/30/29	1	Flexible frame	9 days	L-1	Loss of about $\frac{1}{2}$ (anterior)	Superior	Narrowing	Almost complete	No definite narrowing
15	2/18/30	8	Flexible frame	20 days	D-12	Loss of about $\frac{1}{4}$ (anterior)	Superior	Narrowing	Almost complete	No definite narrowing
16	9/18/30	11	Flexible frame	4 days	D-11	Loss of about $\frac{1}{4}$ (anterior)	Inferior	Narrowing	Almost complete	No definite narrowing

										Gross Fracture-Dislocation				Correction			
										Wedge of Body	Apparent Fracture of Articular Surface	Inter-vertebral Space	Dislocation	Shape of Body	Inter-vertebral Space	Dislocation	
17	10/ 8/29	5	Flexible frame	7 days	L-1	Loss of about 1/2 (anterior)	Superior	No definite narrowing	Almost complete	No definite narrowing							
18	1/ 2/31	1	Flexible frame	3 days	L-1, D-6, 7 and 8	Loss of about 1/2 (anterior) (dorsal vertebrae negligible)	Superior	Slight narrowing	Not complete; still slight wedging								
19	2/11/31	5	Flexible frame	17 days	L-3	Loss of about 1/2 (anterior)	Both	Narrowing	Almost complete								
20	6/ 2/31	8	Flexible frame	About 20 min.	L-2	Loss of about 1/2 (anterior)	Both	Narrowing	Almost complete								
21	2/11/32	12	Flexible frame	About 20 min.	L-1 and 2	Loss of about 1/2 (anterior)	L-1 Superior L-2 Both	Narrowing	No films; next day, pulmonary embolus; recovery								
22	1/29/32	11	Flexible frame	About 20 min.	D-12	Loss of about 1/2 (anterior)	Superior	Narrowing	Almost complete								
23	5/16/32	3	Flexible frame	About 20 min.	L-1	Loss of about 1/2 (anterior)	Both	Narrowing	Almost complete								
24	7/ 6/32	2	Flexible frame	About 20 min.	L-2	Loss of about 1/2 (anterior)	Superior	Narrowing	Almost complete								
Group 3:	9/ 9/30	9	Flexible frame	10 days	L-1	None; sacralization	Both	Narrowing	No change								
	12/27/30	12 wks.	Flexible frame	26 days	L-2	None; sacralization	Superior	Obiteration	No change								
Group 4:	6/21/28	0	Bradford frames	14 days	L-1 and 2	Anterosuperior lip, L-2	Anterosuperior lip only	Obiterated	Anterior L-1 on L-2, about 1/2								
	3/ 5/29	1	Flexible frame	4 days	D-11 and 12	Loss of about 1/2, D-12 (anterior)	Superior	Obiterated	Anterior D-11 on D-12, about 1/2								
28	6/30/29	2	Flexible frame	13 days	D-12, L-1	Loss of about 1/2, L-1 (anterior)	Superior	Obiterated	Anterior and to right D-12 on L-1, about 1/2								
30	9/20/29	23	Flexible frame	15 days	D-11 and 12	Loss of about 1/2, D-11 (anterior)	Superior	Obiterated	Anterior D-11 on D-12, about 1/2								
31	10/23/30	12	Flexible frame	4 days	L-1 and 2	Anterosuperior lip; loss of about 1/2 (anterior)	Superior	No definite narrowing	Almost complete								

being on guard, and served to emphasize the advantage of having the patient conscious during reduction.

It has not been determined definitely how impending or beginning injury to the cord through extension manifests itself. The answer to this question may, however, lie in the experience with these two patients, which seems to indicate that local pain at the site of fracture precedes injury to the cord through reduction, and that loss of reflexes is the next manifestation.

The patient in case 28 (fig. 15) had severe compression fracture of the twelfth dorsal vertebra, associated with forward dislocation of the eleventh dorsal vertebra. Extension was started on the day following the accident. During a very slow extension over a period of four days definite local pain developed at the site of



Fig. 15.—Roentgenograms in case 28: *A*, appearance before reduction; *B*, appearance following reduction; *C*, end-result after four years.

the fracture and dislocation, with decided paralysis of the lower extremities and acute gastro-intestinal symptoms characterized by abdominal distress, vomiting and distention. There was no sphincter disturbance or sensory change. These observations were checked by members of the neurologic staff. Further extension was stopped, and the degree of extension was moderately lessened. After three days, this picture had entirely disappeared, and extension was cautiously resumed. Local pain again developed, and while it was possible slowly to increase the upward convexity of the frame to a slight degree, the pain prevented the accomplishment of any definite increase in extension. Further attempts to complete extension were abandoned. Since this episode, the patient has not had any sign of recurrence of these manifestations.

The patient in case 30 had severe compression of the twelfth dorsal vertebra, with definite forward dislocation of the eleventh dorsal vertebra on the twelfth. The injury occurred twenty-two days before the patient was brought to the service. Extension was started twenty-three days after the injury. It proved

uncomfortable from the start. It was continued until partial reduction was obtained. At this point, the local pain became intolerable and extension was stopped. While the patient revealed no loss of knee jerks and no paralysis, further extension was not forced by the aid of anesthesia, and this was fortunate, for fusion of the spinal cord, which was resorted to at this point, disclosed that the inferior articular processes of the eleventh dorsal vertebra were completely dislocated from their articulating fellows of the twelfth dorsal vertebra, and lay anterior to the latter, that on the right side lying immediately anterior to and locked with the corresponding process of the twelfth dorsal vertebra. Any further extension in this case, it seems, would inevitably have resulted in compression of the cord. Following fusion, this patient made an uneventful recovery and at fourteen months returned to his preinjury activities (chain store manager) without complaint.

In no other patient was there any manifestation of either fleeting or permanent injury to the cord following reduction.

It should be noted, however, that in case 27 (fig. 9), with marked forward dislocation of the first lumbar vertebra on the second, the deformity was reduced without any manifestation of injury to the cord, either during or after reduction.

It seems probable that with careful adherence to the technic described injury to the cord will not occur during reduction in compression fractures uncomplicated by dislocation, in view of the foregoing experience, the mechanics of extension, and the added factor of safety to the cord afforded by the considerable space between it and the walls of the spinal canal in uncomplicated fracture. The definite possibility, however, of injury to the cord during reduction should never be absent from the surgeon's mind, and when dislocation is present, complicating the fracture, it is a real possibility, with local pain possibly the first warning.

#### APPARATUS AND TECHNIC OF FIXATION

The appliance selected for fixation must maintain hyperextension. Otherwise the deformity of the bone will recur (case 6, fig. 16). As the intervertebral disk is usually definitely narrowed or obliterated within one year after the injury, it is of utmost importance to preserve the correction until bone reorganization is adequate. Plaster of paris shells will accomplish this, but they present the decided disadvantage of keeping the patient recumbent, allowing but two positions, prone and supine. The plaster of paris jacket, correctly applied in selected cases, was the most satisfactory form of fixation employed in this series. In favorable cases the patients may be ambulatory from the start, leave the hospital at an early date and may even resume their preinjury activities, if not actually laborious. In this way, general muscle tone is preserved throughout the period of treatment, and morale is decidedly better (fig. 17, case 17).

The patients suitable for ambulatory treatment in a jacket directly after correction are those in whom the fractured vertebra or vertebrae are situated in a portion of the spinal column which is convex forward, as the second, third or fourth lumbar segments. Occasionally, the anterior convexity extends as high as the tenth or eleventh dorsal segment. Such vertebrae, in the erect attitude

and extreme hyperextension of the column, receive the superincumbent weight on the posterior portion of the body (fig. 18). A careful checking of the vertebrae by frequent roentgenograms taken through windows in the jacket has failed to disclose any appreciable loss of bone correction under conditions of constant stress while the wearer was up and about, walking and riding in an automobile. Some ambulatory patients, when overtired, experienced lumbosacral backache (five of twenty-eight, or 18 per cent). Curtailment of activities controlled this complication. One of those so treated began to have, after being up and about for several

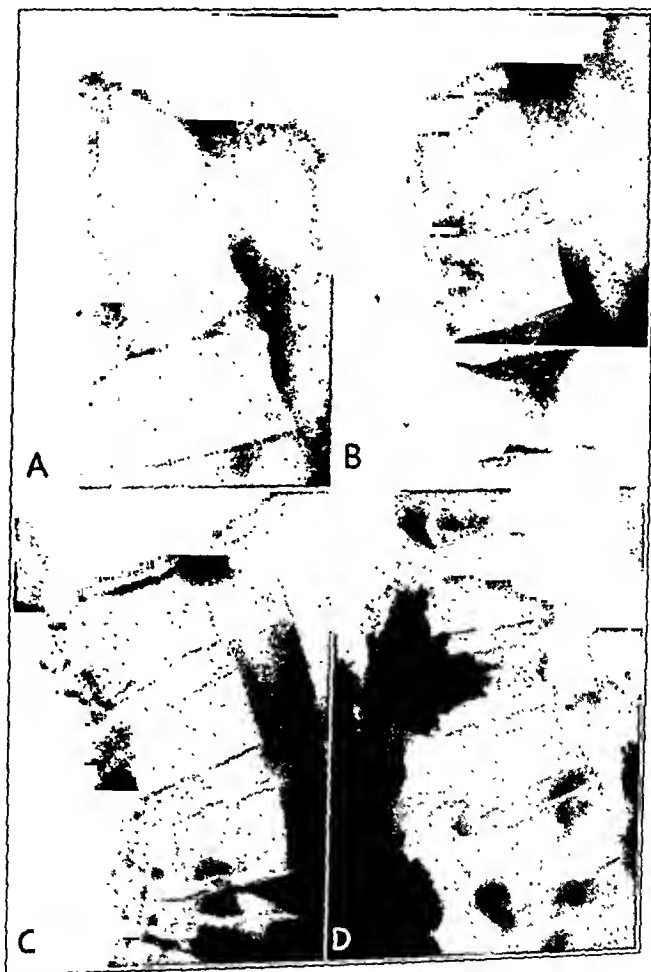


Fig. 16.—Roentgenograms in case 6, in which the correction was lost in a plaster jacket that had become loose owing to the patient's loss of weight: *A*, before reduction; *B*, after reduction; *C*, loss of correction in the jacket; *D*, end-result after sixteen months.

weeks, pain over the posterior sacro-iliac ligaments on one side, with referred pain in the posterior thigh and calf on the same side, requiring that he adopt a less strenuous manner of living. This tendency disappeared on completion of the period of protection of the vertebra and resumption of normal posture.

The patients definitely unsuited to this treatment are those whose fractures lie in the anteriorly concave middle and upper dorsal region (case 16, table 2). This

concavity in some spines extends as far down as the second lumbar vertebra; hence no definite dividing line can be set, but each case must be determined according to the stresses to which the fractured vertebra will be subjected in the hyper-extended position. Patients whose fractures have resulted in crushing of the posterior portion of the centrum or in lateral wedging are obviously not suited to ambulatory treatment. Furthermore, failure is apt to follow such practice in obese persons, and indeed all patients receiving ambulatory treatment should be carefully watched for loss of weight sufficient to allow flexion (case 6, fig. 16). A jacket which for any cause is loose should be removed and either a new one applied or the ambulatory treatment abandoned. Probably a jacket on a recumbent patient maintains correction in all vertebrae up to and possibly including the eighth dorsal. My experience in this manner of fixation is too limited to state—two patients—in both of whom correction was preserved until reorganization of the



Fig. 17.—Roentgenograms in case 17: *A*, spinal column while patient was under ambulatory treatment in a jacket applied directly after reduction and worn six months; *B*, the end-result after two years and four months.

bone was complete (fig. 19, case 20). It seems to be a question when recumbency is demanded which is more acceptable to the patient, a jacket or shells.

The support of corrected vertebrae in cases unsuited to jackets, and in cases of spinal fusion, is conveniently afforded by plaster shells. Patients in such cases should be placed immediately on a regimen of exercises: active extension for the maintenance and development of the erectores spinae, abdominal retraction and deep breathing, and for the lower extremities mild "goose-stepping."

*Technic of the Application of a Jacket.*—The patient, with spine fully hyper-extended and torso equipped with shirt or stockinet and protected by felt, is partially suspended while still on the frame by the small webbed square, already described, under the lumbar region (fig. 14). Heavy felt padding is essential. Two thicknesses of half inch (1.27 cm.) saddlers' felt are used over the spinal

column and one layer of fourth inch (0.64 cm.) or thicker felt over the iliac crests and about the upper part of the thorax, as shown in figure 21 *B* and *C*. Goldthwaite irons, adjusted to fit the contour of the hyperextended spine, are then placed beneath the patient's torso, the suspending canvas sling is removed, and the plaster applied (fig. 20). This simplification is a convenience. Equally practical it is to transfer the patient at the completion of extension to the standard form of Goldthwaite irons as shown in figure 21. The jacket should be about one-fourth inch thick. It is extended as high as the suprasternal notch, is applied snugly over the entire anterior wall of the chest and is molded snugly to the iliac

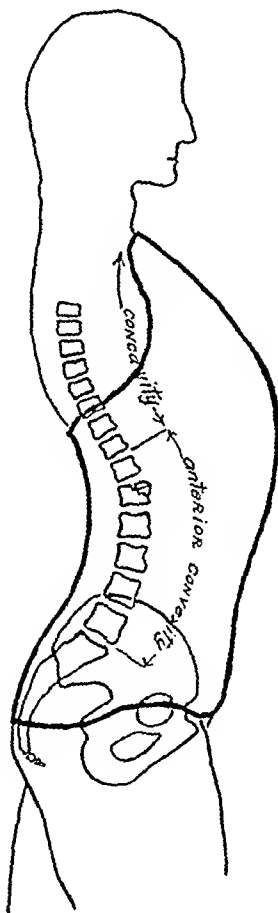


Fig. 18.—Drawing showing the type of patient suited to ambulatory treatment in a jacket. The fractured vertebra (or vertebrae) is situated in a portion of the spinal column which is convex forward. Such a vertebra in the erect attitude and extreme hyperextension of the column receives the superincumbent weight on the posterior portion of the body.

crests, reaching as far down as about one-half inch below the anterior superior iliac spines. Posteriorly, it fits snugly into the lumbar lordosis and extends from the spines of the scapulae to half way down the sacrum. Three areas of accurate contact should thus result, two anteriorly, namely, the anterior wall of the chest and the anterior portion of the iliac crests, and one posteriorly, the lumbar region. When dry, the jacket is trimmed, and the patient is returned to bed.

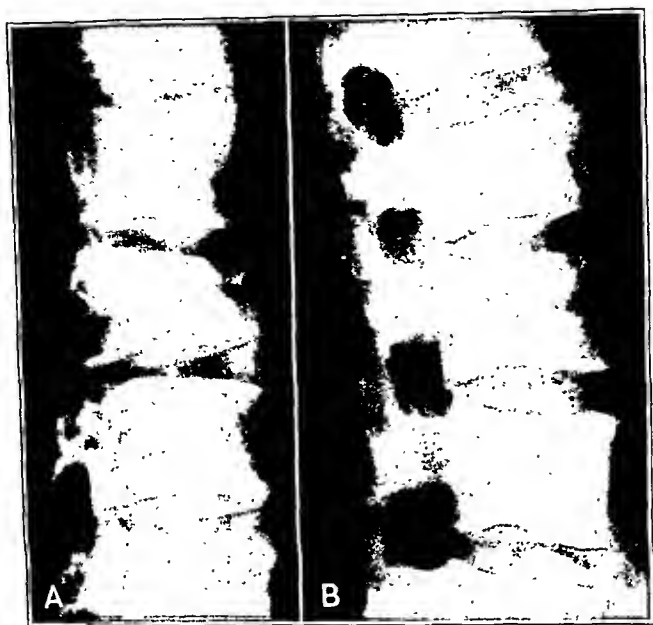


Fig. 19.—Roentgenograms illustrating maintenance of correction during recumbency in a jacket: *A*, before reduction; *B*, after four months of recumbency in a jacket.

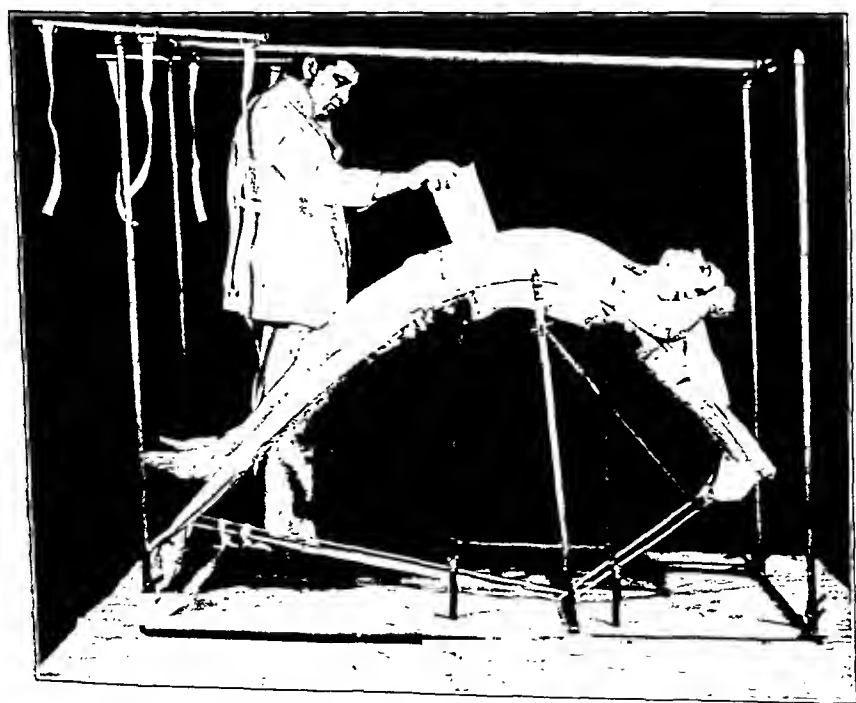


Fig. 20.—Here a plaster jacket has been applied following reduction.



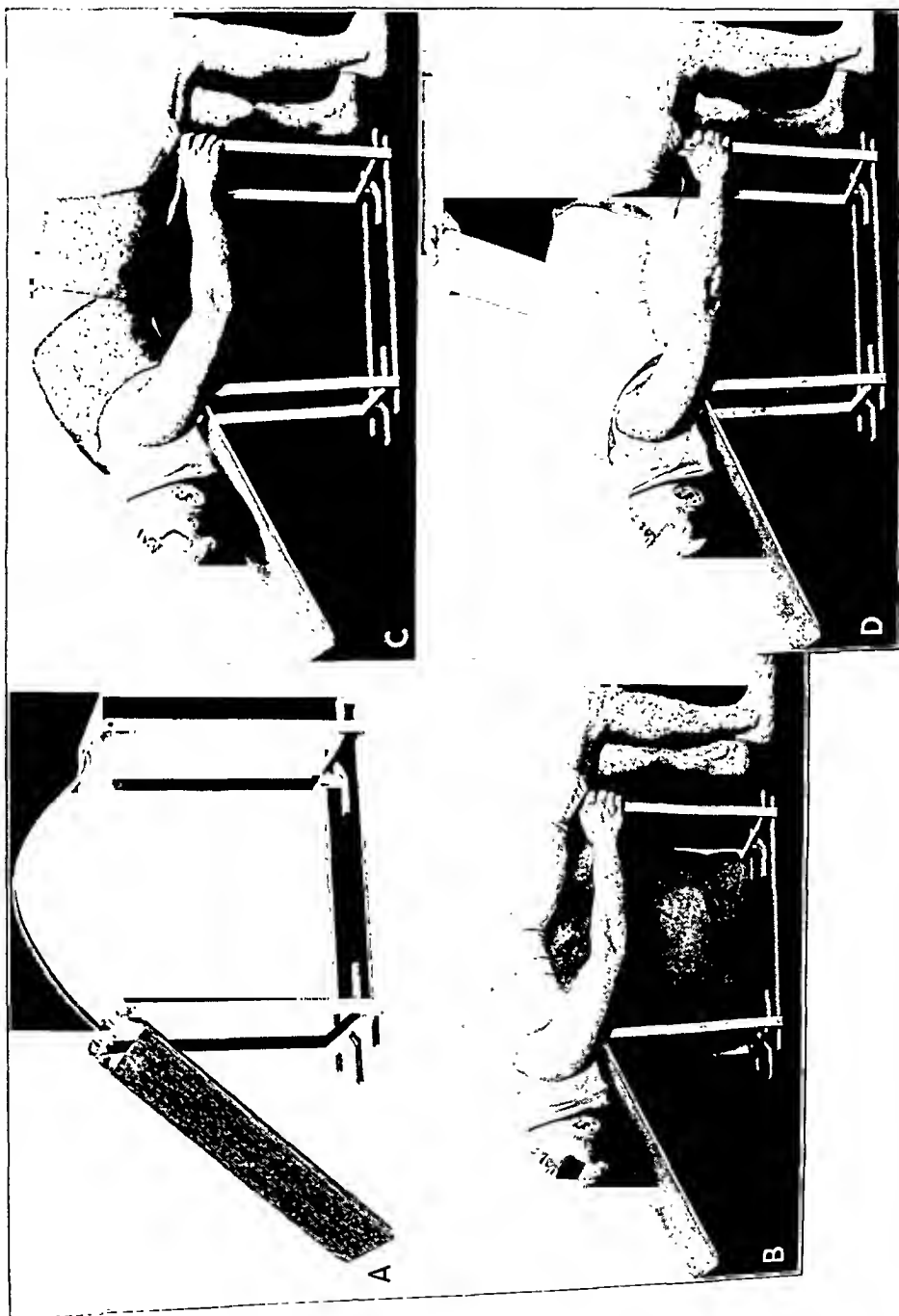


Fig. 21.—*A*, the Goldthwaite irons used in application of the plaster jacket; *B* and *C*, arrangement of sadiers' felt; *D*, application of the jacket.

It is well to place the patient on a diet of fluids and give a daily enema for forty-eight hours following correction and application of the jacket. Otherwise, gastro-intestinal upsets are common; in two patients in this series adynamic ileus developed. In the very slender and the old, it may be necessary to split the jacket in the midline anteriorly and spread it a little to allay a distressing feeling of smothering, evidently associated with the extreme expansion of the chest. Both patients with ileus promptly lost their symptoms following this procedure. Later the jacket may be brought together and wrapped, or wrapped less tightly, with several layers of plaster bandage. Windows cut the following day in the sides of



Fig. 22.—The completed jacket, ready to have windows cut in it opposite the fracture.

the jacket, opposite the fracture, make possible roentgenographic interpretation of progress (fig. 22). It has been the custom to have roentgenograms taken the day following the application of the jacket, one week afterward, and if these were satisfactory, once a month thereafter until reorganization of the bone seemed assured.

Following the period of fixation in plaster, which lasts until reorganization of the bone is assured (from two to seven months), a high spring steel back-brace is applied while the patient is in the hyperextended position. This is worn

while the patient is up and about, and is removed when he is recumbent. Extension exercises are vigorously pushed at this stage, so that in from one to two months the erectores spinæ are powerful and fully capable of performing their task. The brace is worn until the strength of the muscles is definitely adequate, usually from the fifth to the seventh month, and is then gradually discarded over a period of from two to three weeks. A deep lumbar lordosis remains which must be corrected before the active stage of treatment can be regarded as over. If it is not corrected, the patient is theoretically fully as liable to strain and fatigue as if the fractured vertebra had not been corrected. This may be accomplished in from two to four weeks, or more, varying with the patient's age and ability to cooperate. Exercises in lumbar flexion are given to stretch contracted lumbar soft parts, and the patient is instructed in pelvic control and the habitual carriage of the pelvis in the vertical position. The restoration of back mechanics and the repair of the fracture being completed, it is simply a question of general development when the successful return to preinjury activities may be expected.



Fig. 23.—Roentgenograms in a case of nuclear prolapse (case 24): *A*, before reduction; *B*, after reduction; *C*, nuclear prolapse at seven months.

#### RESULTS IN THIRTY-ONE FIXATIONS (TABLE 2)

*Jacket-Recumbency.*—Eight patients whose fractures were fixed by recumbency in a jacket for from one to seven days suffered no loss of correction of either vertebral body or intervertebral space. Four others so treated for three weeks, six weeks, two and four months, respectively, likewise retained full correction.

*Jacket-Ambulatory.*—Fourteen patients were rendered ambulatory in jackets from one to seven days following the correction, and this type of fixation was continued for from two to seven months, varying with the severity of their deformity and apparent disorganization of the bone (an average of four and one-half months). Of this group two lost the bone correction (cases 6 and 16). In the others, bone correction

was maintained. The patient in case 6 (fig. 16), after almost complete correction, was discharged from the hospital seven days following reduction, having been ambulatory for three days, with orders to return for checkup at two week intervals. She did not report until thirteen weeks later, when she had lost about 20 pounds (9.1 Kg.) and her jacket was quite loose through that circumstance. Roentgenograms disclosed the loss of correction. In retrospect, she should not have been selected for ambulatory treatment because of her initial obesity and the site of her fracture, the twelfth dorsal vertebra, which in her case lay at the beginning of the anteriorly concave dorsal curve, and because of the doubt of her willingness to come in for frequent observation. The patient in case 16, likewise ill-selected for ambulatory-jacket care, could not, through circumstances, be closely watched, and she lost her correction following a second and unsatisfactory application of a jacket.

The fate of the intervertebral space was, however, quite different. There was definite narrowing during this period in three patients, marked narrowing in three, and the space was lost, of course, in the two patients in whom bone correction was not maintained. In only six patients were both bone and space correction maintained. Of these, it should be stated that three lost their spaces subsequent to bone repair and termination of fixation, and one showed a slight narrowing of the space at two years and four months, which was evidently to remain indefinitely by reason of a complete and heavy bridge of bone.

*Shells.*—Shells were used in eleven cases, and the restoration of both bone and space was preserved throughout their period of fixation.

#### FATE OF INTERVERTEBRAL DISK AND FRACTURED VERTEBRAL BODY (TABLE 3)

The inevitable alteration in structure of the disk following extensive injury was clearly demonstrated at Schmorl's clinic. With alteration in structure there ensues change in function in the form of loss of adaptability to changing stresses and of resistance to "wear and tear." Local mechanics are no longer adequate to demands, and compensatory structural changes slowly develop similar to those observed in other injured weight-bearing joints, namely, narrowing of the joint space, proliferative bone changes at the margins of the joint and increased bone density. These changes and their development may be easily followed by means of a series of roentgenograms of the patient, taken monthly at first and then at six month intervals. Figure 6 illustrates the changes in a typical case. They vary with age, occupation and previous condition of the joints.

*Spur Formation.*—This occurred in eighteen cases, or 60 per cent, and was first noted at various times from five weeks to four and one-

TABLE 2.—Summary of Experience in Thirty-One Fixations

Group and Case	Date	Vertebra Involved	Type of Fixation			Loss of Correction		Type of Fixation		Loss of Correction		Type of Fixation		Loss of Correction	
			First	Time		Verte-bral Body	Inter-verte-bral Space	Second	Time	Verte-bral Body	Inter-verte-bral Space	Third	Time	Verte-bral Body	Inter-verte-bral Space
Group 1:															
1	9/17/29	L-1	Jacket, recumbent	6 days		None	None	Jacket, ambulatory	8 wks.	None	None	Third	Time	None	None
2	4/ 8/30	L-2	Jacket, recumbent	2 mos.*		None	None	Jacket, ambulatory	2 mos.	None	None	High back-brace	3 mos.	None	None
3	12/18/30	D-8	Jacket, recumbent	1 day		None	None	Jacket, ambulatory	2 wks.	None	None	High back-brace	6 mos.	None	None
4	3/30/31	L-1, 2, 3 and 4	Jacket, recumbent	1 day		None	None	Jacket, ambulatory	4 mos.	None	None	Jacket, ambulatory	5 mos.	None	None
5	7/23/31	L-1	Jacket, recumbent	6 wks.†		None	None	Jacket, ambulatory	2 mos.	None	None	High brace	7 wks.	None	No further narrowing
6	10/ 4/31	D-12	Jacket, recumbent	5 days		None	None	Jacket, ambulatory	4 mos.	Cor- rection lost†	Marked narrowing	High brace	3 mos.	None	Very slight narrowing
7	11/12/31	D-12, L-1	Jacket, recumbent	5 days		None	None	Jacket, ambulatory	4 mos.	None	Marked narrowing	High brace	2 mos., then inter-mittent	Complete narrowing	Marked narrowing
8	11/12/31	L-2	Jacket, recumbent	4 days		None	None	Jacket, ambulatory	5 mos.	None	Marked narrowing	High brace	6 wks.	None	Definite narrowing
9	7/23/28	L-3, L-4	Jacket, recumbent		No correction	None	None	Jacket, ambulatory	10 wks.	None	Very slight narrowing	High brace	7 wks.	None	Very slight narrowing
10	9/29/28	L-1	Shells (fusion operation; jacket, recumbent)	5 wks.‡		None	None	Jacket, ambulatory	8 wks.	None	None	High brace	4 wks.	None	Definite narrowing at 6 mos.
11	1/23/29	D-12	Shells	8 wks.		None	None	Jacket, ambulatory	2 mos.	None	Very slight narrowing	High brace	5 mos.	None	Marked narrowing
12	3/ 4/29	D-12	Shells	8 wks.		None	None	Jacket, ambulatory	6 wks.	None	Very slight narrowing	High brace	6 wks.	None	Very slight narrowing
13	3/ 9/29	D-11	Shells	5 wks.		None	None	Jacket, ambulatory							



TABLE 3.—*Röntgenographic Changes*

Graphic Changes																
Case	Date	Vertebra Involved	Age	Occupation	Before	Spurring			Time of Apparent Union	Time of Loss of Intervertebral Space*				Apparent Nuclear Prolapse		
						First Noted	New Spur Formation			First Noted	During Flexion		Time		Amount	Complete
							Still Increasing	Bridging Complete			Flexion	After Flexion				
1	9/17/29	L-1	31	Salesman	None	None (3 yrs., 5 mos.)	.....	.....	Indeter- minate	None	None (3 yrs., 5 mos.)	.....	.....	None		
2	4/ 8/30	L-2	64	Bricklayer	Extensive D-10 and L1, moderate lumbar	None (2 yrs., 9 mos.)	.....	.....	4 mos.	None	None (2 yrs., 9 mos.)	.....	.....	None		
3	12/18/30	D-8	22	Telephone linesman C†	None	None (2 yrs.)	.....	.....	2-5 mos.	2 wks.	.....	.....	.....	Slight L-4 (first noted 2 yrs., 9 mos.)		
4	3/30/31	L-1, 2, 3 and 4	23	Longshore- man, C	None	None (1 yr., 11 mos.)	.....	.....	4 mos.	None	None (1 yr., 11 mos.)	.....	.....	.....		
5	7/23/31	L-1	56	Janitor	None	None (1 yr., 6 mos.)	.....	.....	4-7 mos.	None	Between 7-13 mos.	.....	.....	.....		
6	10/ 4/31	D-12	50	Housekeeper	Moderate lateral	None (1 yr., 4 mos.)	.....	.....	4-7 mos.	4 mos.	.....	.....	.....	.....		
7	11/12/31	L-2	56	Bulldozer	None	None (1 yr., 1 mo.)	.....	.....	2½ mos.	None	Between 5-7 mos.	.....	.....	.....		
8	11/12/31	L-2	56	Bulldozer	None	Slight (14 mos.)	.....	.....	5 mos.	None	Between 1 yr., 2 mos.)	.....	.....	.....		
9	7/25/28	L-3	22	Carpenter	None	None	.....	.....	3 mos.	.....	.....	.....	.....	.....		
10	9/29/28	L-4	36	Carpenter	None	6 mos.	.....	.....	Indeter- minate	.....	.....	.....	.....	.....		
11	1/28/29	D-12	39	Freight handler, C	None	8 mos.	.....	.....	15 wks.	.....	.....	.....	.....	.....		
12	3/ 4/29	D-12	36	Housewife	None	.....	.....	.....	Indeter- minate	.....	.....	.....	.....	.....		
13	3/ 9/29	D-11	44	Sportswoman	Slight slipping L-1 and 2	.....	.....	.....	None	.....	.....	.....	.....	.....		
14	11/30/29	L-1	41	Fireman, C	None	6 mos.	.....	.....	3½ mos.	.....	.....	.....	.....	.....		
						3 yrs., 2 mos.	.....	.....	None (4 mos.)	.....	.....	.....	.....	.....		
						.....	.....	.....	3½-5 mos.	.....	.....	.....	.....	.....		
						.....	.....	.....	3 wks.	.....	.....	.....	.....	.....		
						.....	.....	.....	.....	.....	.....	.....	.....	.....		
						.....	.....	.....	.....	.....	.....	.....	.....	.....		
						.....	.....	.....	.....	.....	.....	.....	.....	.....		
						.....	.....	.....	.....	.....	.....	.....	.....	.....		
						.....	.....	.....	.....	.....	.....	.....	.....	.....		
						.....	.....	.....	.....	.....	.....	.....	.....	.....		
						.....	.....	.....	.....	.....	.....	.....	.....	.....		
						.....	.....	.....	.....	.....	.....	.....	.....	.....		
						.....	.....	.....	.....	.....	.....	.....	.....	.....		
						.....	.....	.....	.....	.....	.....	.....	.....	.....		
						.....	.....	.....	.....	.....	.....	.....	.....	.....		
						.....	.....	.....	.....	.....	.....	.....	.....	.....		
						.....	.....	.....	.....	.....	.....	.....	.....	.....		
						.....	.....	.....	.....	.....	.....	.....	.....	.....		
						.....	.....	.....	.....	.....	.....	.....	.....	.....		
						.....	.....	.....	.....	.....	.....	.....	.....	.....		
						.....	.....	.....	.....	.....	.....	.....	.....	.....		
						.....	.....	.....	.....	.....	.....	.....	.....	.....		
						.....	.....	.....	.....	.....	.....	.....	.....	.....		
						.....	.....	.....	.....	.....	.....	.....	.....	.....		
						.....	.....	.....	.....	.....	.....	.....	.....	.....		
						.....	.....	.....	.....	.....	.....	.....	.....	.....		
						.....	.....	.....	.....	.....	.....	.....	.....	.....		
						.....	.....	.....	.....	.....	.....	.....	.....	.....		
						.....	.....	.....	.....	.....	.....	.....	.....	.....		
						.....	.....	.....	.....	.....	.....	.....	.....	.....		
						.....	.....	.....	.....	.....	.....	.....	.....	.....		
						.....	.....	.....	.....	.....	.....	.....	.....	.....		
						.....	.....	.....	.....	.....	.....	.....	.....	.....		
						.....	.....	.....	.....	.....	.....	.....	.....	.....		
						.....	.....	.....	.....	.....	.....	.....	.....	.....		
						.....	.....	.....	.....	.....	.....	.....	.....	.....		
						.....	.....	.....	.....	.....	.....	.....	.....	.....		
						.....	.....	.....	.....	.....	.....	.....	.....	.....		
						.....	.....	.....	.....	.....	.....	.....	.....	.....		
						.....	.....	.....	.....	.....	.....	.....	.....	.....		
						.....	.....	.....	.....	.....	.....	.....	.....	.....		
						.....	.....	.....	.....	.....	.....	.....	.....	.....		
						.....	.....	.....	.....	.....	.....	.....	.....	.....		
						.....	.....	.....	.....	.....	.....	.....	.....	.....		
						.....	.....	.....								





half years. In sixteen of these eighteen cases there was narrowing of the intervertebral space; in two, narrowing was not definite. Of the latter two, one was that of a man, aged 56, doing laborious work; in the other there had been surgical fusion. Eight other patients showed marked narrowing but spurs did not develop. Of these eight, three were 15, 22 and 24 years of age, respectively; three were women of light activities; one had not had roentgenograms taken, because of other illness confining her to bed, and in the fifth the narrowing was too recent (nine months). With loss of the intervertebral disk and alteration of the size and shape of the vertebral body, local mechanics are inadequate and these proliferative reparative changes ensue.

TABLE 4.—*Time for Complete Bridging of Intervertebral Space*

Case	Time of Recognition	Case	Time of Recognition
31.....	4 mos.	20.....	18 mos.
23.....	8 mos.	19.....	2 yrs.
30.....	8 mos.	27.....	3 yrs. and
26.....	13 mos.		4 yrs., 6 mos.
11.....	14 mos.	12.....	4 yrs.
29.....	15 mos.	10.....	4 yrs., 4 mos.

TABLE 5.—*Narrowing of Intervertebral Space*

Narrowing of Space	Number of Cases	Percentage
Slight.....	3	10
About $\frac{1}{2}$ .....	10	32
About $\frac{2}{3}$ .....	2	6
About $\frac{3}{4}$ .....	2	6
Complete.....	9	29

*Complete Bridging of Intervertebral Space by Bone.*—This condition apparently resulted in fusion in eleven of twenty-six cases, or 42 per cent, as shown by roentgenograms. The time of probable completion of the bridge across the intervertebral spaces varied widely (table 4).

*Narrowing of Intervertebral Space.*—This change occurred in twenty-six cases, or 84 per cent. In only five was it absent, in one of which a spinal fusion was performed. No fracture of the articular surface was demonstrated in one of these five, and there probably was none, since the disk did not become narrow. I am unable to explain it in the other three, other than to assume that the cartilaginous end-plates escaped fracture, although they seemed not to have done so.

*Nuclear Prolapse.*—This condition was apparent or questionable in ten cases, or 32 per cent (figs. 15 and 23).

*Bone Reorganization.*—This condition was indeterminate by roentgenogram in ten patients, definite in nineteen in from two to seven

months, varying with the degree of disorganization of the bone, and in two other patients, with badly shattered centra, in from four to eight and eight to eleven months, respectively.

#### END-RESULTS (TABLE 6)

*Restoration to Preinjury Activities.*—Twenty patients, or 65 per cent, returned successfully to preinjury activities and remained free from pain. They returned in from two to fourteen months (the average was eight and a third months). Of this number, eight would probably generally be regarded as having had severe fractures, nine, moderately severe and three, mild. Three of the nine patients with severe fractures had surgical fusion. Five of the twenty patients were in the industrial compensation class.

*Restoration of Light Activities.*—Six patients returned successfully to lighter activities, five at from five to eleven months and one at twenty-seven months. Four of these patients do light work because of pain in the back on doing laborious work steadily. Of the other two, one (case 3) prefers clerical work to hard labor; the other (case 21, eleven months after injury) has been instructed not to do heavy work yet. In three, the fracture healed and was reduced; in one, an excellent reduction was obtained but later was lost during fixation (case 6) and in two there was no correction.

*Failure to Return to Work.*—Table 7 presents the facts regarding patients who have not resumed former occupations.

*Fractures of Posterior Bony Processes.*—Roentgenograms showed fracture in the bony processes, exclusive of the transverse processes, in only five of the thirty-one cases. They were confined to the articular processes and laminae. Doubtless, many were not detected. Fracture of the pedicles was not diagnosed in the entire series; five of the patients showed fractures in one or more transverse processes.

#### SPINAL FUSION

It may be seen that the restoration of the shape of the vertebral body and of the intervertebral space obtained by hyperextension reestablishes the preinjury anteroposterior spinal curves. This restoration is only partially maintained in a high percentage of cases (84 per cent in this series) through the loss of some or all of the intervertebral disk. It is also apparent that a large proportion (65 per cent in this series) of these patients with correction return to preinjury activities, free from symptoms, in from two to fourteen months in spite of this loss. This bespeaks a high degree of adaptability of the back as a whole to whatever loss in statics narrowing of the disk produces.

TABLE 6.—End-Results

Case	Verte-bra	Age	Occupation*	Complica-tions	Lumbosacral Junction	Estimate of Cor-rection	Surgical Fusion	Period Apparent of Fixa-tion	Correction of Body	Estimated Loss of Inter-vertebral Space	Return to Light Activ-ities†	Return to Preliminary Activ-ities†	Symptoms; Nature of Disability	Time of Em-ploy-ment Result
1	L-1	31	Salesman	None	No defects	Almost complete	None	9 wks.	None	None	.....	2 mos.	None	3 yrs., 3 mos.
2	L-2	64	Bricklayer	Fracture of ankle	Marked spurting	Almost complete	None	4 mos.	None	None	.....	.....	None; cannot get work	2 yrs., 10 mos.
3	D-8	22	Telephone linesman, C	None	No defects	Almost complete	None	5½ mos.	None	About ½	6 mos. (clerical)	.....	None	2 yrs.
4	L-1, 2, 3	23	Longshoreman, C	Sprain condylar fracture of femur	Failure of fusion, neural arch, 1st sacral	Almost complete	None	4 mos.	None	None	11 mos. (clock tender)	.....	Pain in muscles in lower part of back on doing heavy lifting	1 yr., 10 mos.
5	L-1	56	Janitor	Fracture of os calcis	No defects	Almost complete	None	4 mos.	None	Slight	.....	7 mos.	None	1 yr., 6 mos.
6	D-12	50	Housekeeper	None	Narrowing L-5 intervertebral space	Almost complete	None	4 mos.	None	About ¾	6 mos.	.....	Still wears brace; aches in muscles of lower part of back after much hard work	1 yr., 4 mos.
7	D-12 L-1	33	Registered nurse	None	No defects	Almost complete	None	4 mos.	None	About ½	.....	3 mos.	None	1 yr.
8	L-2	56	Builder	None	No defects	Almost complete	None	5 mos.	None	None	6 mos.	9 mos.	None	1 yr., 2 mos.
9	L-3 L-4	22	Carpenter, O	None	No defects	None	None	None	None	About ½ (both)	None	None	Aches in muscles in lower part of back when tired	3 yrs., 6 mos.
10	L-1	36	Carpenter	None	No defects	Almost complete	D-12 L-1 and 2	4½ mos.	Yes	Maintained	About ½	8 mos.	None	4 yrs., 4 mos.
11	D-12	39	Freight-handler, C	None	No defects	Almost complete	None	4 mos.	Yes	Maintained	About ¾	.....	None	4 yrs.

	12	D-12	76	Housewife	Fracture of lamina and superior articular process, D-12	No defects	Almost complete	None	4 mos.	Yes	Maintained	Complete	.....	10 mos.	None	3 yrs., 11 mos.
13	D-11	41		Sports- woman	None	No defects	Almost complete	None	4½ mos.	None	Maintained	Marked	.....	4 mos.	None	3 yrs., 10 mos.
14	L-1	41		Fireman, O	Fracture of transverse process, L-1	No defects	Almost complete	None	4 mos.	None	Maintained	Complete	2 wks. (telephone operator)	7 mos.	None	3 yrs., 2 mos.
15	D-12	63		Cook	Synphysis, arterio- sclerosis	Partial sacraliza- tion, L-5 transverse process	Almost complete	None	4 mos.	None	Maintained	Complete	.....	9 mos.	None	2 yrs., 11 mos.
16	D-11	53		Housewife	Fracture of left ulna, Kynlund's disease	No defects	Almost complete	None	4 mos.	Not known	Lost during fixation period	Complete	.....	10 mos.	Ache in mus- cles in lower part of back when tired	2 yrs., 4 mos.
17	L-1	51		Farmer	Fracture of radius	No defects	Almost complete	None	6 mos.	Prob- able	Maintained	Slight	1 mo.	7 mos.	None	2 yrs., 4 mos.
18	L-1	21		Sports- woman	None	No defects	Almost complete	None	3 mos.	None	Maintained	Complete	.....	10 mos.	None	2 yrs.
19	L-3	50		Monthbaker, O	Adolescent dorsal kyphosis; fracture of transverse process, L-1 and 5;	No defects	Almost complete	L-2 and 3	6 mos.	Yes	Maintained	Slight	5 mos. (over- seer)	Not yet to full activities	Dorsal pain intermittently	1 yr., 11 mos.
20	L-2	47		Sleeple- Jack, L†	Extensive fracture of both ankles L-2 articular process (?); old scoliosis	Old scol- iosis	Almost complete	None	4 mos.	Yes	Maintained	Upper ¼, lower ¾	None	None	Back "stiff," no pain, halus rigidus	1 yr., 7 mos.
21	L-1, 2	49		R. R. freight conductor, O	Fracture of pelvis, transverse processes L-2 and 3	Partial sacraliza- tion L-5 transverse process	.....	None	None	None	None	Upper ¼, lower com- plete	11 mos.	.....	None	1 yr.
22	D-12	46		Housewife	None	No defects	Almost complete	None	5½ mos.	.....	Maintained	About ½	.....	9 mos.	None	10 mos.

\* In this column, O means that compensation was sought. L means lumbar, and D, dorsal.  
† From date of injury.

TABLE 6.—End-Results—Continued

Verte- Case	Age	Occupation*	Comple- tions	Lumbosacral Junction	Estimate of Cor- rection	Surgical Fusion	Period Apparent of Fusa- tion Bridg- ing	Correction of Body	Estimated Loss of Inter- vertebral Space	Return to Light Activ- ities†	Return to Preinjury Activ- ities†	Symptoms; Nature of Disability	Time of End- Result
23	L-1	Tree sur- geon's assis- tant, C	None	No defects	Almost complete	None	4 mos.	Malnathned	Upper $\frac{2}{3}$ , lower $\frac{1}{2}$	.....	.....	None	9 mos.
24	L-2	Student	None	No defects	Almost complete	None	4 mos.	.....	Upper $\frac{1}{2}$ , lower $\frac{1}{4}$	.....	7 mos.	None	8 mos.
25	L-1	Station fire- man, C	None	Horizontal sacrum	No change	None	6 mos.	Yes	None	2½ mos.	9 mos.	None	2 yrs., 5 mos.
26	L-2	Porter, C	Fracture of pelvis, wrists and femur	Failure of fusion of 1st sacral neural arch	No change	None	7 mos.	Yes	None	8 mos.	13 mos.	Aches in mus- cles in lower part of back when tired	2 yrs.
27	L-1, 2	Milkman, C	Fracture of transverse processes L-1, 2 and 3	Failure of fusion of 1st sacral neural arch	Almost complete	L-1, 2 and 3	3 mos.	Yes	Maintained	About ½	9 mos.	None	4 yrs., 7 mos.
28	D-11, 12	Serub- woman, C	None	No defects	Partial correc- tion	None	7½ mos.	None	Maintained	Complete	10 mos. (house- work)	Has not tried	"Tires" in lower 3 yrs., part of back, 10 mos. no pain
29	D-12, L-1	Mechanic, L	Fracture of superior articular process and lamina L-1	Failure of fusion of 1st sacral neural arch	No change	None	2½ mos.	Yes	None	Complete	15 mos. (chauff- eur)	Tried and failed	Pain in muscles in lower part of back on prolonged heavy labor
30	D-11, 12	Chain store manager	None	No defects	Slight correc- tion	D-11 and 12 and L-1	6 mos.	Un- known	Maintained	About ½	14 mos.	None	2 yrs., 4 mos.
31	L-1, 2	Mechanic	Fracture of transverse process L-2, superior articular process (?)	No defects	Almost complete	None	3½ mos.	Yes	Maintained	About ½	5 mos.	None	2 yrs., 3 mos.

\* In this column, C means that compensation was sought. L means lumbar, and D, dorsal.  
† From date of injury.

The nature of the adaptive changes indicates, however, an effort on the part of the tissues to establish an ankylosis at the site of injury which, as shown by roentgenogram, seems not infrequently to be successful. If such effort is uniformly and demonstrably inadequate, the need of help, as by spinal fusion, is indicated. Furthermore, the increase in the anteroposterior spinal curves resulting from the loss of the disk leaves a mechanical situation which is to some degree less sound and to which the patient must always accommodate himself in the future.

The results in these cases, at least over a period of from two to five years, lead one to believe that such practice is not indicated as a routine procedure. When permanence in an almost complete restoration of mechanics is desired, the procedure should be limited to fusing the corrected vertebra to its fellow opposite the disk whose narrowing is inevitable.

Operative spinal fusion following correction and before much narrowing of the disk occurred resulted in the permanence of most of the

TABLE 7.—Data on Patients Who Have Not Returned to Preinjury Activities

Case	Correction	Reason
2	Almost complete	Cannot find work
9	None attempted	Low backache
20	Almost complete	Painful hallux rigidus and fused ankles; is a steeplejack
23	Almost complete	Too early (9 months)
28	Partial	Because of litigation

intervertebral space in four cases in this series which would otherwise have been lost. In these cases the postreduction mechanics of the back have remained practically constant throughout two, four and four and a half years, respectively (figs. 5 and 9). Its practice should not unduly prolong the total convalescence, but recumbence will be considerably lengthened in cases otherwise suited to jacket and ambulatory care. Its advantages in preserving better mechanics must be weighed against the disadvantages of added cost, a period of hospitalization, the risk of operative intervention and the possible detriment to the patient's morale. I believe it was definitely indicated only in cases partially corrected in group 4 (the fracture-dislocation group), and possibly in group 3. In such cases, it should be practiced with the spine in extension and the fusion made to include that vertebra above whose superior surface is parallel with the inferior surface of the fractured vertebra, or the one below, if the inferior intervertebral space is narrowed (usually four in all). Six months should be allowed for the completion of the fusion. Intensive corrective exercises are then essential, if freedom from backache is to be assured. The deep lumbar lordosis, habitual after six months, must be eliminated, as in the case in which no fusion is performed.

## SUMMARY

1. Recent fractures of the vertebral body can be corrected so as to reestablish preinjury mechanics of the back (96 per cent in this series).
2. Recent fracture and dislocation are more difficult of reduction (40 per cent in this series).
3. Part of this correction is usually lost (84 per cent in this series) through the ultimate gradual narrowing of the injured intervertebral disk.
4. The back is capable of a remarkable degree of adaptability to this change (65 per cent returned to preinjury activities in eight and a third months, as an average, and remained free from symptoms).
5. Reorganization or union of bone occurred in all cases, and is probably fully adequate in from two to seven months in most cases.
6. Correction may be lost through inadequate fixation.
7. The mechanics of correction through hyperextension are demonstrated.
8. The risk of injury to the cord through hyperextension is probably confined to cases of fracture and dislocation, and is probably not great, with care, in these.
9. Passing interruption of function of the cord occurred during hyperextension in one case of fracture and dislocation and manifested itself as a loss of reflexes and a motor paralysis of the lower extremities for several days.
10. Complete bridging of bone across the intervertebral region occurs in a large number of cases (42 per cent in this series) and may be apparent as early as four months and up to four and a half years.
11. Spinal fusion in extension is indicated in cases of fracture with dislocation when adequate correction cannot be obtained.

# THE SCHILLING HEMOGRAM IN APPENDICITIS

HERBERT A. CARLSON, M.D.

AND

LUCRETIA WILDER, B.S.

MINNEAPOLIS

All clinicians agree that the diagnosis of appendicitis must rest on an interpretation of the clinical history and the physical signs rather than on a laboratory test. However, surgeons have often been impressed with the lack of correlation between the clinical manifestations of appendicitis and the observations at operation and the microscopic pathologic aspect of the appendix. Any laboratory test which aids in preoperative differentiation between inflammatory and noninflammatory conditions or which can serve as an index of the severity of the infection should prove of value.

It is desirable that the stage, severity and complications of appendicitis be determined as accurately as possible before operation. This is particularly important in clinics where the conservative (Ochsner) treatment is employed in selected cases. In this connection the history and physical signs are of foremost importance. The duration of symptoms, the change in the character, location or severity of the pain and the presence or absence of a mass or of generalized or localized tenderness, rigidity or rebound tenderness are all factors to be studied critically in forming an opinion regarding the pathologic process present and the plan of treatment to be pursued. The pulse rate and the temperature provide additional information as to the severity of the disease.

Widely divergent opinions have been expressed concerning the value of blood counts in the diagnosis of appendicitis. Disagreement is to be expected, as some authors have referred to the leukocyte count alone, others have included the Ehrlich<sup>1</sup> differential count, and recently more complete methods of examination of the blood film, such as the Schilling hemogram, have been investigated. There is no point in discussing the value of the leukocyte count alone. It is sufficient to mention that Finney<sup>2</sup> found a leukocyte count below 10,000 in only 8 per cent of a series of 1,162 patients including those with acute appendicitis and appendicitis with abscess or peritonitis.

---

From the Department of Surgery, University of Minnesota.

1. Ehrlich, L., quoted by Harter and Lyons.<sup>7</sup>

2. Finney, J. M. T., Jr.: Appendicitis: Some Observations Based on Review of Three Thousand, Nine Hundred and Thirteen Operative Cases, *Surg., Gynec. & Obst.* 56:360, 1933.



The differential count now commonly used, which classifies cells into lymphocytes, monocytes, polymorphonuclears, eosinophils and basophils, was first formulated in 1891 by Ehrlich. In 1904 Arneth<sup>3</sup> discovered that the variations in the nuclear structure of the polymorphonuclear leukocytes can be correlated with the severity of the disease. He made an extensive classification of the neutrophils according to the number of lobes and their shape. In all there are more than eighty classes of leukocytes. This count was too complicated for routine clinical application, but it paved the way for further studies. In 1912 a satisfactory simplification of the Arneth index was devised by Victor Schilling.<sup>4</sup> He divided the neutrophils into four classes according to the state of immaturity of the nucleus. The four groups consist of: myelocytes; juvenile forms, which are the metamyelocytes of Pappenheim; stab or band forms having no definite nuclear lobulations, and mature segmented cells. Other modifications of the Arneth count have been originated by Cooke, Piney and Farley.

The surgical application of the Schilling hemogram has been the subject of recent papers by Yaguda,<sup>5</sup> Luck,<sup>6</sup> Harter and Lyons,<sup>7</sup> Goodale and Manning<sup>8</sup> and Fitz-Hugh,<sup>9</sup> who agreed essentially that the Schilling index is of more clinical value than the older Ehrlich method in detecting the presence, the degree and the persistence of infection.

It is not the purpose of this article to discuss the technic of making the Schilling count or its biologic significance, as these subjects have been covered by Schilling, Bredeck,<sup>10</sup> Yaguda and others. An excellent but brief review of the Arneth count, the Schilling hemogram and other modifications of the Arneth count is to be found in a recent contribution by Fitz-Hugh, who emphasized the limitations of these methods. It is sufficient to state here that the Schilling hemogram is a relatively simple means of recording the reaction of the bone marrow to infection or to toxic stimuli. In this count the lymphocytes, monocytes, eosinophils and

---

3. Arneth, J., quoted by Schilling.<sup>4</sup>

4. Schilling, V.: *The Blood Picture*, St. Louis, C. V. Mosby Company, 1928.

5. Yaguda, A.: *Studies on Schilling Count in Appendicitis*, *Am. J. Clin. Path.* **1**:39, 1931.

6. Luck, J. V.: *Schilling Differential Blood Count in Appendicitis*, *Am. J. Surg.* **19**:275, 1933.

7. Harter, J. S., and Lyons, C.: *Surgical Applications of the Schilling Differential Blood Count*, *Surg., Gynec. & Obst.* **56**:182, 1933.

8. Goodale, R. H., and Manning, N. E.: *The Schilling Index in Appendicitis*, *J. Lab. & Clin. Med.* **16**:386, 1931.

9. Fitz-Hugh, T., Jr.: *Present Day Modifications of the Arneth Count in Surgical Practice: A Clinical Review*, *Internat. S. Digest* **15**:195, 1933.

10. Bredeck, J. F.: *The Schilling Blood Differential Count in Tuberculosis*, *Am. Rev. Tuberc.* **20**:52, 1929.

basophils are listed as in the Ehrlich differential count, but the neutrophils are further classified into segmented forms, stab cells, juvenile cells and myelocytes. In infectious diseases neutrophils enter the blood stream in earlier stages of development than normally, so that there is an increase in the number of stab cells and juvenile cells, and even myelocytes may appear, the presence of the latter indicating a severe infection. The increase in the number of nonsegmented neutrophils in the circulating blood is referred to as a shift to the left.

A standard normal Schilling hemogram may be found in tables 1 to 6, but it should be noted that variations may occur in normal persons. Fitz-Hugh said, "We consider the normal adult non-filament<sup>11</sup> count to be between four and ten per cent of the total leukocytes and would not be willing to draw any weighty deductions from a 'shift' of less than ten per cent magnitude."

In interpreting the blood picture the total leukocyte count, the percentage of neutrophils, lymphocytes, monocytes and eosinophils and the degree of shift to the left must all be given consideration. The total leukocyte count is generally believed to be an indication of the resistance of the body to infection. The percentage of neutrophils and the shift to the left correspond to the severity of the infection. The percentage of lymphocytes, monocytes and eosinophils decreases as the infection becomes more severe and increases as the infection subsides.

Yaguda, from a study of 671 cases in which the Schilling index was correlated with the histologic observations on the appendix, concluded (1) that the presence of a normal percentage of immature forms rules out a diagnosis of appendicitis; (2) that a count of immature cells of less than 14 per cent indicates a mild process, probably limited to the mucosa; (3) that a count of immature cells of more than 14 per cent indicates diffuse suppurative appendicitis of increasing severity as the count approaches 30 per cent; (4) that a count of immature forms of more than 35 per cent indicates perforation with peritonitis, and (5) that repeated counts are of definite prognostic value.

Although we were skeptical about the possibility of determining the exact pathologic process present by the degree of shift to the left, we undertook the study of the blood count on a series of 107 patients to estimate the value of the hemogram; as a means of differentiating between appendicitis and other conditions causing pain in the right lower quadrant; as a means of differentiating simple acute appendicitis from appendicitis complicated by abscess or peritonitis, and as a prognostic aid in serious conditions. In this investigation the patients were studied clinically by one of us (H. A. C.); all the blood studies were made by the other (L. W.).

---

11. Nonsegmented.

For purposes of comparison the patients were classified in five separate groups (tables 1 to 6). In group 1 (19 patients) were placed all those for whom the pathologist returned a diagnosis of inactive appendicitis. Most of the patients in this group had had recurrent attacks characteristic of appendicitis. One patient had no physical signs of appendicitis, but an interval appendectomy was performed on the advice of the referring physician. In 6 patients, tenderness in the right lower quadrant was the only physical sign. In 1 patient who had both cholecystectomy and appendectomy, it was found at operation that the symptoms had been due chiefly to hydrops of the gallbladder.

In group 2 (13 patients), in which the condition was designated as "mild appendicitis," were placed the patients who showed some slight change, such as peritonitis of the appendix, subacute appendicitis or mild acute appendicitis. It is recognized that there were some patients in this group for whom the diagnosis of appendicitis might be questioned. In others the condition undoubtedly represented the subsiding stage of acute suppurative appendicitis.

In group 3 (41 patients) were included all those with unquestioned acute suppurative appendicitis with no preoperative complications. The diagnosis was confirmed by operation and by microscopic examination of the appendix. In some of the patients in this group the appendix had patches of gangrene, and in some instances the peritoneal cavity contained clear or even turbid fluid, but none of the patients showed definite evidence of perforation or of peritonitis.

In group 4 (25 patients) were placed those who showed clinical evidence of local peritonitis or formation of an abscess. Conservative treatment was the rule in this group. However, all but 1 patient ultimately had either an appendectomy or drainage of an abscess.

In group 5 (9 patients) were included the patients with general peritonitis. One patient was operated on elsewhere seven days previous to admission to the University of Minnesota Hospital. She had diffuse peritonitis at the time of admission. Another patient had perforation at operation, with free pus in the peritoneal cavity. Operation was deferred in all the other cases. The only deaths in the entire series were the 3 which occurred in this group. The diagnosis of peritonitis complicating appendicitis was confirmed at necropsy in 2 of the 3 fatal cases, and in the third there was diffuse peritonitis, appendectomy having been performed elsewhere.

At least one Schilling count was made on each patient in the series. The count was usually made immediately on admission to the hospital. Repeated counts were made on some of the patients, particularly on those having abscess or peritonitis, so that the Schilling hemograms could be correlated with the clinical progress.

#### OBSERVATIONS

The age of the patient, the duration of symptoms, the temperature on admission, the pulse rate and the Schilling hemogram are tabulated (tables 1 to 6). Maximum, minimum and average values are given. The terms maximum and minimum refer to the highest and lowest values under each heading, not to the highest or lowest recorded for any one patient.

*Group 1 (table 1).*—The average leukocyte count, the average number of neutrophils and the average Schilling count in this group were all within normal limits. In only 6 of the 19 patients were the nonsegmented forms in excess of 10 per cent.

TABLE 1.—Readings for Nineteen Patients in Group 1, with Inactive Appendicitis

	Age, Years	Duration of Symptoms	Temperature, F.	Pulse Rate
Maximum.....	59	30 days	99.5	120
Minimum.....	12	10 hours	97.4	60
Average.....	29	5 days	98.6	85

	Schilling Hemogram						Seg- mented Cells	Lym- pho- cytes	Mono- cytes	Total Poly- morpho- nuclears
	White Blood Cells	Baso- phils	Eosino- phils	Myelo- cytes	Jure- niles	Stab Cells	51 to 67	21 to 35	4 to 8	51 to 72
Standard	7 to 9,000	0 to 1	2 to 4	0	0 to 1	3 to 5	76	51	2	50
Maximum	13,600	1	12	1	5	21	76	51	2	50
Minimum	6,450	0	0	0	0	3	37	19	0	46
Average	9,576	0.05	2	0.05	1	8	60	27	0.5	70

The high leukocyte count with neutrophils and the shift to the left noted in some of the patients who had no demonstrable pathologic process in the appendix was probably due to the fact that the symptoms and signs were caused by some infectious process other than appendicitis. The Schilling count in this group was not always of value, because it could not be used to differentiate appendicitis from some other mild infection. However, it is worth while to notice that the shift to the left was usually slight if present. In some instances the Schilling hemogram was normal when leukocytosis was found to be present. Therefore the hemogram correlated more closely than the total white cell count with the appendical pathologic process. The following observations on 2 patients are examples:

Patient	White Blood Cells	Baso- phils	Eosino- phils	Myelo- cytes	Jure- niles	Stab Cells	Seg- mented Cells	Lym- pho- cytes	Mono- cytes	Total Poly- morpho- nuclears
I. F.	12,000	0	0	0	0	3	65	31	1	68
L. L.	12,600	0	1	0	1	5	74	19	0	80

Two patients in this group had eosinophilia. One, with 7 per cent eosinophils, had psoriasis, and the other, with 12 per cent eosinophils, vomited an ascaris following the appendectomy.

*Group 2 (table 2).—*The patients with mild appendicitis had average leukocyte counts and average neutrophil counts within the range of normal. The Schilling hemogram showed great variation, but the average count exceeded the upper limit of normal. Of the individual counts, 6 showed more than 10 per cent nonsegmented cells and 7, 10 or less. One patient in this group had a definite shift to the left, with 21 per cent stab and 6 per cent juvenile cells. This patient was reported to have peritonitis of the appendix. It is difficult to correlate the clinical and pathologic observations in this heterogeneous group, but it may be said that the pathologic evidence of appendicitis was not always conclusive and the changes in the blood picture were usually slight or absent.

*Group 3 (table 3).—*The correlation between the blood picture and the demonstrated pathologic changes was striking in this group of 41 patients with acute suppurative appendicitis. Thirty-eight had total leukocyte counts over 10,000, and 37 had more than 75 per cent of neutrophils. In 3 patients there were fewer than 10 per cent of nonsegmented neutrophils. Only 1 patient had a normal blood picture in the entire series of 41. This was a patient with subsiding appendicitis, the blood count having been made when the patient entered the hospital five days after the onset of symptoms.

TABLE 2.—Readings for Thirteen Patients in Group 2 with Mild Appendicitis, Subacute Appendicitis and Peritonitis of the Appendix

	Age, Years	Duration of Symptoms	Temperature, F.	Pulse Rate
Maximum.....	26	30 days	102.6	102
Minimum.....	9	6 hours	98.2	70
Average.....	17	5 days	99.2	93

	Schilling Hemogram									
	White Blood Cells	Baso- phils	Eosino- phils	Myelo- cytes	Juve- niles	Stab Cells	Seg- mented Cells	Lym- pho- cytes	Mono- cytes	Total Poly- morpho- nuclears
Standard	7 to 9,000	0 to 1	2 to 4	0	0 to 1	3 to 5	51 to 67	21 to 35	4 to 8	54 to 72
Maximum	13,950	4	4	0	6	21	76	46	2	85
Minimum	6,100	0	0	0	0	5	31	15	0	52
Average	9,385	0.4	0.9	0	2	10	58	28	0.8	70

TABLE 3.—Readings for Forty-One Patients in Group 3 with Acute Suppurative Appendicitis

	Age, Years	Duration of Symptoms	Temperature, F.	Pulse Rate
Maximum.....	70	14 days	103.0	135
Minimum.....	7	10 hours	98.0	60
Average.....	23	46 hours	99.6	95

	Schilling Hemogram									
	White Blood Cells	Baso- phils	Eosino- phils	Myelo- cytes	Juve- niles	Stab Cells	Seg- mented Cells	Lym- pho- cytes	Mono- cytes	Total Poly- morpho- nuclears
Standard	7 to 9,000	0 to 1	2 to 4	0	0 to 1	3 to 5	51 to 67	21 to 35	4 to 8	54 to 72
Maximum	24,600	1	2	3	5	31	77	48	3	95
Minimum	7,150	0	0	0	0	2	44	5	0	51
Average	15,310	0.02	0.2	0.3	2	17	63	16	0.5	63

The hemograms of 2 patients who had practically normal Schilling counts but an increase in the total number of leukocytes and some increase in the number of neutrophils are:

Patient	White Blood Cells	Baso- phils	Eosino- phils	Myelo- cytes	Juve- niles	Stab Cells	Seg- mented Cells	Lym- pho- cytes	Mono- cytes	Total Poly- morpho- nuclears
J. G.	19,300	0	0	0	0	7	69	21	3	76
L. S.	14,300	0	0	0	1	9	77	13	0	87

Even in these examples, including two of the three lowest counts for nonsegmented cells in group 3, the percentage of stab cells was increased above the normal standard.

The advantage of the Schilling count over the Ehrlich differential count is illustrated in the following case in which the leukocyte count and the percentage of lymphocytes and neutrophils were normal:

A. O. had acute suppurative appendicitis with bands of adhesions producing partial strangulation of the small intestine. The fluid in the peritoneal cavity showed streptococci and staphylococci on culture. The Schilling count was:

White Blood Cells	Baso- phils	Eosino- phils	Myelo- cytes	Juve- niles	Stab Cells	Seg- mented Cells	Lym- pho- cytes	Mono- cytes	Total Poly- morpho- nuclears
8,450	0	0	0	2	22	44	32	0	63

In the case of O. S. the Schilling hemogram was of more significance than the white blood cell count or the percentage of neutrophils.

White Blood Cells	Baso- phils	Eosino- phils	Myelo- cytes	Juve- niles	Stab Cells	Seg- mented Cells	Lym- pho- cytes	Mono- cytes	Total Poly- morpho- nuclears
10,000	0	2	2	3	21	51	15	3	77

The following count is an example of the unreliability of the leukocyte count alone. The patient, S. S., postoperatively became seriously ill with signs of peritonitis. The increased shift to the left was a much more accurate index of the clinical course. The patient recovered.

Date	White Blood Cells	Baso- phils	Eosino- phils	Myelo- cytes	Juve- niles	Stab Cells	Seg- mented Cells	Lym- pho- cytes	Mono- cytes	Total Poly- morpho- nuclears
4/28	13,250	0	0	0	4	15	74	7	0	93
Immediate operation on 4/28										
5/1	8,800	0	0	0	2	40	49	9	0	91

Experience with the Schilling hemogram in acute suppurative appendicitis indicates that a decided shift to the left may occur when the total leukocyte count and the total neutrophil count are normal. On the other hand, in some instances definite leukocytosis may be present when the Schilling count is not significantly altered. If a complete study of the blood is made, some alteration of the blood picture indicating the presence of infection will almost always be found in the active stage of acute suppurative appendicitis.

TABLE 4.—Readings for Twenty-Five Patients in Group 4 with Appendicitis with Local Peritonitis or Abscess

	Schilling Hemogram										
	White Blood Cells	Baso- phils	Eosino- phils	Myelo- cytes	Juve- niles	Stab Cells	Seg- mented Cells	Lym- pho- cytes	Mono- cytes	Total Poly- morpho- nuclears	
Maximum.....					71	30 days	102.6			136	
Minimum.....					7	20 hours	98.0			60	
Average.....					37	6 days	100.5			103	
Standard	7 to 9,000	0 to 1	2 to 4	0	0 to 1	3 to 5	51 to 67	21 to 35	4 to 8	54 to 72	
Maximum	29,050	1	2	4	5	44	51	40	2	95	
Minimum	9,400	0	0	0	0	9	37	5	0	59	
Average	17,458	0.04	0.2	0.4	2	20	60	13	0.6	86	

Group 4 (table 4).—Great variations were noted in the leukocyte count, in the total number of neutrophils and in the degree of shift to the left in the patients of this group. This was to be expected, as the group included patients with various stages of local peritonitis and formation of abscesses. Only 2 patients had a leukocyte count of less than 10,000, and 4 had a normal percentage of neutrophils. Three had a Schilling hemogram showing less than 10 per cent of non-segmented forms, but in these the duration of the disease varied from two weeks to more than a month.

Changes of the blood picture occurring in 1 patient (E. P.) as the clinical picture changed from that of local peritonitis to that of a walled-off appendical abscess are illustrated.

Date	White Blood Cells	Baso-phils	Eosino-phils	Myelo-cytes	Juve-niles	Stab Cells	Seg-mented Cells	Lym-pho-cytes	Mono-cytes	Total Poly-morpho-nuclears
6/29	11,000	0	0	0	1	24	58	7	0	93
7/ 1	6,550	0	0	1	2	47	39	10	1	89
7/ 5	10,600	0	0	3	4	33	48	12	0	88
7/ 9	11,150	0	0	0	0	20	62	17	1	82
7/12	7,800	0	0	0	0	6	55	38	3	61

The abscess was drained on July 13, one day after the last examination of the blood.

The two hemograms which were taken on 1 patient (F. S.), one on his first admission to the hospital when he had an appendical abscess and the other a month later when he returned for appendectomy, were as follows:

Date	White Blood Cells	Baso-phils	Eosino-phils	Myelo-cytes	Juve-niles	Stab Cells	Seg-mented Cells	Lym-pho-cytes	Mono-cytes	Total Poly-morpho-nuclears
3/6	11,900	0	1	4	4	26	37	28	0	71
4/4	6,800	0	0	0	0	10	61	28	1	71

The white cell count was elevated in the first instance, but if an Ehrlich differential count had been done a mild infection would have been indicated. In this case the Schilling count was a much more accurate index of the severity of the patient's condition.

The great variations noted in this group confirm rather than oppose the idea that a shift to the left is related to the severity of the infection, as it was only in old subsiding conditions that normal counts were obtained. The counts showing the highest number of nonsegmented neutrophils were invariably in patients in the acute stage of local peritonitis or formation of an abscess. Some of the abscesses were drained subsequently. Some patients had appendectomies after several weeks of conservative treatment, and usually at operation there were numerous adhesions indicating previous peritonitis.

TABLE 5.—Readings for Nine Patients in Group 5 with Appendicitis with Diffuse Peritonitis

		Age, Years	Duration of Symptoms	Temperature, F.	Pulse Rate
Maximum.....		50	10 days	102.4	140
Minimum.....		5	56 hours	98.0	92
Average.....		25	5 days	100.9	117

Schilling Hemogram										
	White Blood Cells	Baso-phils	Eosino-phils	Myelo-cytes	Juve-niles	Stab Cells	Seg-mented Cells	Lym-pho-cytes	Mono-cytes	Total Poly-morpho-nuclears
Standard	7 to 9,000	0 to 1	2 to 4	0	0 to 1	3 to 5	51 to 67	21 to 35	4 to 8	54 to 72
Maximum	37,800	0	1	3	7	55	73	24	5	95
Minimum	5,450	0	0	0	2	23	15	5	0	76
Average	14,950	0	0.1	0.9	4	40	44	10	0.7	89

Group 5 (table 5).—The Schilling counts on the 9 patients with diffuse peritonitis showed a marked shift to the left, although in some instances the total number of leukocytes was normal. In this group the blood picture invariably indicated a severe infection at some period of observation.

For example, L. S. had an appendectomy performed elsewhere seven days prior to admission to the hospital. On admission there were signs of diffuse peritonitis. The patient died the following day. The blood count was:

White Blood Cells	Baso- phils	Eosino- phils	Myelo- cytes	Juve- niles	Stab Cells	Seg- mented Cells	Lym- pho- cytes	Mono- cytes	Total Poly- morpho- nuclears
6,000	0	0	2	4	55	15	24	0	76

Another hemogram is given to show the changes occurring in the blood of a man (J. L.) operated on for acute appendicitis with early perforation and peritonitis. After operation he showed signs of diffuse peritonitis, but he ultimately recovered. The hemograms were:

Date	White Blood Cells	Baso- phils	Eosino- phils	Myelo- cytes	Juve- niles	Stab Cells	Seg- mented Cells	Lym- pho- cytes	Mono- cytes	Total Poly- morpho- nuclears
7/27	15,650	0	0	0	4	23	68	5	0	95
8/ 3	7,550	0	0	0	4	47	29	20	0	80
8/12	13,300	0	0	1	0	24	61	14	0	86
8/21	7,300	0	0	0	1	12	68	19	0	81

Three deaths occurred in this group. The hemograms showed a marked shift to the left, but no difference could be detected between the counts on those who survived and those who died. The series of counts for E. C. shows that survival may occur, even when the Schilling hemogram indicates a bad prognosis.

E. C., aged 39 years, was admitted on June 21, 1933, with a history suggesting appendicitis with perforation of the appendix. The clinical picture was that of diffuse peritonitis. The patient was treated conservatively. On July 5 and September 5 pelvic abscesses were drained. The hemograms were:

Date	White Blood Cells	Baso- phils	Eosino- phils	Myelo- cytes	Juve- niles	Stab Cells	Seg- mented Cells	Lym- pho- cytes	Mono- cytes	Total Poly- morpho- nuclears
6/22	5,450	0	0	0	4	47	37	12	0	83
6/23	4,850	0	0	3	6	47	29	15	0	85
6/27	13,150	0	1	0	4	31	51	13	0	86
6/30	14,100	0	1	0	6	45	36	12	0	87
7/ 3	13,250	0	0	1	7	53	27	12	0	88
7/ 7	11,200	0	1	0	5	29	45	17	0	82
7/12	9,350	0	1	0	2	12	61	22	2	75
7/17	19,000	0	0	0	4	20	63	13	0	87
7/31	9,750	0	0	0	1	34	48	17	0	83
8/12	12,000	0	0	0	4	33	40	23	0	77
8/19	9,150	0	2	0	3	20	42	33	0	65

The patient was dismissed from the hospital much improved after drainage of the two abscesses.

TABLE 6.—Comparison of the Averages of Schilling Count, Pulse Rate and Temperature of the Five Groups

	White Blood Cells	Basophil	Eosinophil	Myelocytes	Juveniles	Stab Cells	Segmented Cells	Lymphocytes	Monocytes	Total Polymor- phonuclears	Temperature, F.	Pulse Rate
Standard	7 to 9,000	0 to 1	2 to 4	0	0 to 1	3 to 5	51 to 67	21 to 33	2 to 4	54 to 72	98.6	80
Group 1	9,576	0.05	2.0	0.05	1	8	60	27	0.5	70	98.6	85
Group 2	9,335	0.4	0.9	0.0	12	10	58	25	0.8	70	99.2	93
Group 3	15,310	0.02	0.2	0.3	12	17	63	16	0.5	83	99.6	95
Group 4	17,458	0.04	0.2	0.4	12	20	60	13	0.6	86	100.5	100
Group 5	14,950	0.0	0.1	0.9	4	40	44	10	0.7	89	100.9	117



TABLE 7.—*Temperature on Admission to the Hospital*

	Group 1, 10 Patients	Group 2, 13 Patients	Group 3, 41 Patients	Group 4, 25 Patients	Group 5, 9 Patients
99 F. or under.....	14	10	14	5	1
99.1 to 100 F.....	5	1	15	6	0
100.1 to 101 F.....	0	1	10	4	3
101.1 to 102 F.....	0	1	1	8	3
102.1 to 103 F.....	0	0	1	2	2

TABLE 8.—*Pulse Rate on Admission to the Hospital*

	Group 1, 10 Patients	Group 2, 13 Patients	Group 3, 41 Patients	Group 4, 25 Patients	Group 5, 9 Patients
80 or less.....	7	1	10	1	0
81 to 100.....	10	10	19	13	4
101 to 120.....	2	2	8	9	1
121 to 140.....	0	0	4	2	4

## COMMENT AND SUMMARY

In this study we found an increase of the average shift to the left for each succeeding group of patients, beginning with the patients with an inactive appendix and ending with those with acute appendicitis and diffuse peritonitis. Variations of the blood picture occurred within each group, but in a general way they corresponded with the clinical variations which also occurred within each group; that is, when the appendicitis was clinically mild or subsiding the blood counts approached more nearly the normal and when the disease was active and more severe greater shifts from the normal occurred. We do not propose to attempt to diagnose appendicitis or to differentiate its stages or gauge its severity entirely on the number or percentage of any type of blood cell, but we believe that when considered with the history, physical signs, temperature and pulse rate, the Schilling differential blood count is of real value in differentiating between inflammatory and noninflammatory conditions and in estimating the severity of the disease. In this respect it is decidedly of more value than the leukocyte count alone, and it is also of more value than the Ehrlich differential count.

In tables 1 to 6 are given the maximum, minimum and average temperature and pulse rate (recorded on admission to the hospital for comparison with the hemogram). In tables 7 and 8 is given more detailed information regarding the temperature and pulse rate of the patients in the various groups. Both the temperature and the pulse rate showed great variation, and the temperature especially was unreliable in providing evidence of the presence of infection or in enabling one to judge the seriousness of the infection present. The pulse rate appeared to be a slightly better index of the severity of the infection but as 29 of 41 patients in group 3, 14 of 25 patients in group 4 and 4 of 9 patients in group 5 had a pulse rate of 100 or less, and as some patients in each

of the three groups had a pulse rate over 120, the pulse rate cannot be called a delicate test of the severity of the infection. It is our opinion that the Schilling hemogram is of greater independent value than either the temperature or the pulse rate in estimating the severity of the infection present.

#### CONCLUSIONS

The Schilling hemogram is superior to the total leukocyte count and to the Ehrlich differential count in estimating the presence or severity of infection.

In appendicitis the Schilling hemogram is a better index of the severity of the disease than either the temperature or the pulse rate.

A marked shift to the left may indicate a bad prognosis, but not necessarily a fatal one. Some patients who survived showed greater shifts than others who died.

In clinics where conservative treatment is employed in appendicitis with perforation or in subsiding appendicitis, the Schilling hemogram should be an aid in determining the stage and severity of the disease and in following its progress.

# RELATION OF ARTERIES TO ROOTS OF NERVES IN POSTERIOR CRANIAL FOSSA IN MAN

JAMES CRAWFORD WATT, M.D.  
Professor of Anatomy, University of Toronto

AND

ANGUS NEIL McKILLOP, M.B.  
Demonstrator of Anatomy, University of Toronto  
TORONTO, CANADA

The removal of a portion of the occipital bone has become a well established and frequently used surgical method of approach in operations on certain of the cranial nerves. The posterior cranial fossa is opened on the side indicated, and the roots of the nerves may be identified as they pass from the brain toward their exit through the dura mater and the cranial foramina.

The sensory root of the trigeminal nerve may thus be exposed and sectioned for the relief of tic douloureux. For a similar intense glossopharyngeal neuralgia, the ninth cranial nerve may be reached and cut. By the same route the vestibular portion of the acoustic nerve has been divided to provide relief from the intolerable vertigo of Ménière's disease.

In all of these procedures surgeons have encountered certain hazards and complications which have added considerably to the difficulty of performing the operation successfully. One of the most serious dangers is that of hemorrhage due to the cutting or the injuring of a blood vessel which may lie either on the nerve to be sectioned or in close proximity to it.

Arteries not described in the ordinary textbook of anatomy are sometimes encountered lying on the nerves which are to be divided. In other cases large arterial trunks may exhibit flexures which bring them into the field of an operation in which they are not usually present. Here they may provide obstructions which prevent the surgeon from obtaining a clear route to the structure he wishes to reach, and they are in serious danger of being wounded. They may, of course, be ligatured or clipped, but no surgeon voluntarily disposes of them in this manner, as he may immediately precipitate serious symptoms by the deprivation of a part of the brain of its blood supply. In saving the artery from injury, he may encounter considerable added difficulty in performing the operation successfully.

Recognizing the conditions just enumerated, we undertook an investigation of the variations of the arteries lying in the posterior cranial fossa. Extensive work has been accomplished, the results of which

are later to be published in full. It was thought desirable, however, to report in a separate paper the facts referring to the relation of the arteries and the nerve roots which we had obtained, since this information is of special value to the neurologic surgeon.

The observations recorded in the present paper are the results of the study in approximately sixty cases of the arteries supplying the hindbrain. Thirty-five brains were obtained from bodies in the dissecting room; the rest were secured at autopsy and were immediately preserved in a dilute solution of formaldehyde. The material used was in good condition. Since records were made only of the vessels which could be followed definitely and accurately, a complete record of all of the arteries of each brain was not made.

We observed, as has been previously noted by many other workers, that the right and the left vertebral artery were frequently unequal in size and unsymmetrical in course. The level of their union to form the basilar artery varied considerably, from the normal position at the lower limit of the pons to one a few millimeters above or 1.5 cm. below this location. The length of the basilar artery thus varied considerably. Variations also appeared in its course; it was sometimes curved or tortuous to a marked degree and was displaced from the median line. All of these changes have been frequently noted before. As they are not of such immediate clinical application to surgical procedures with nerve roots as are the other observations reported in this paper, no detailed description of them will be given here.

#### INVESTIGATIONS

The relation of the blood vessels to the roots of the cranial nerves in the posterior cranial fossa is reviewed in the order of the occurrence of the nerves, beginning with the fifth or trigeminal nerve.

*Trigeminal Nerve.*—A constant branch arising from the anterior part of the basilar artery was observed coursing transversely across the pons and passing to the ventral surface of the sensory root of the trigeminal nerve. This vessel (figs. 4, 6, 7, 8, 9 and 10) was sometimes of considerable size. Stopford<sup>1</sup> also noted it in many of his preparations. Being situated ventral to the nerve root, it is sheltered and is not visible to the surgeon. Thus it is in danger of being divided with the nerve in an operation for the relief of tic douloureux, which involves the division of the entire sensory root of the fifth nerve. This artery apparently supplies the nerve root and the semilunar ganglion. The vessel is not mentioned in the textbooks; we therefore suggest the term "trigeminal artery."

1. Stopford, J. S. B.: The Arteries of the Pons and Medulla Oblongata, J. Anat. & Physiol. 50:131 and 255, 1915-1916.

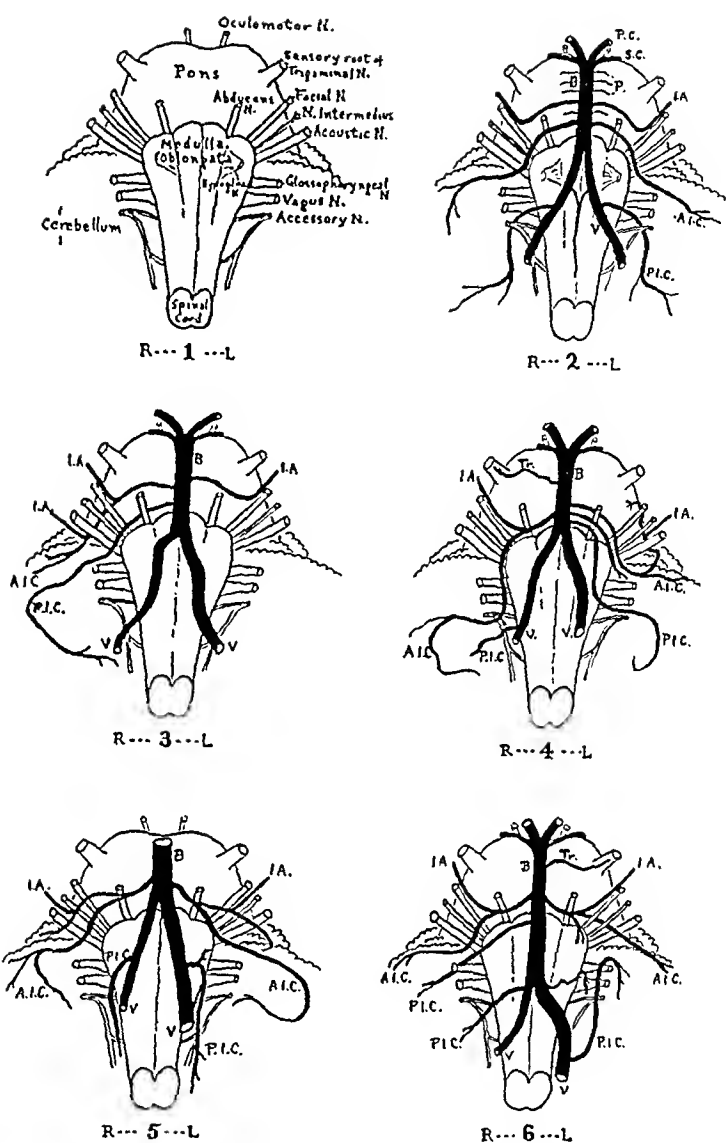
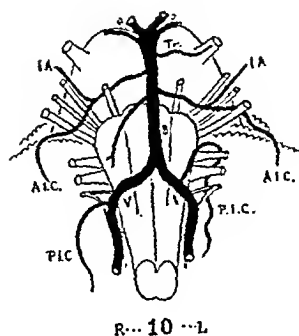
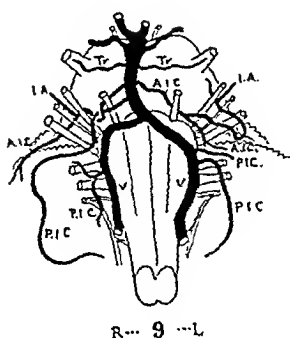
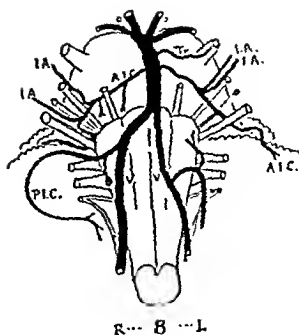
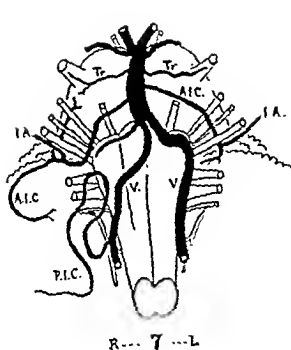


Fig. 1.—Key sketch showing inferior surface of cerebellum, pons and medulla oblongata with roots of third to twelfth cranial nerves.

Fig. 2.—Idealized scheme of vertebral and basilar arteries and their branches, based on textbook descriptions. Arterial branches are equal and symmetrical; internal auditory artery is shown arising on basilar; anterior inferior cerebellar artery crosses ventral to roots of abducent, facial and acoustic nerves, and posterior inferior cerebellar artery, on its way to cerebellum, passes ventral to roots of glossopharyngeal, vagus and accessory nerves or through interval between latter two. In this diagram and in figures 3 to 10, *R* denotes the right side and *L*, left side. Arteries are designated as follows: *A.I.C.* is anterior inferior cerebellar; *B.*, basilar; *I.A.*, internal auditory; *P.*, pontile; *P.C.*, posterior cerebral; *P.I.C.*, posterior inferior cerebellar; *S.C.*, superior cerebellar; *Tr.*, trigeminal, and *V.*, vertebral.

Figs. 3 to 10.—Arterial relations noted in cases studied. Diagrams illustrate all possible positions of internal auditory, anterior inferior cerebellar and posterior inferior cerebellar arteries. Trigeminal artery is shown in several instances. Complete descriptions of these arteries and their relations to nerve roots are contained in the text.



Dorsal  
Medial 2 3 5 3 → Lateral  
Facial N. ① ② ③ Acoustic N.  
11 24 16 10 2  
Ventral

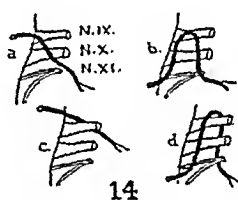
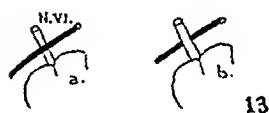
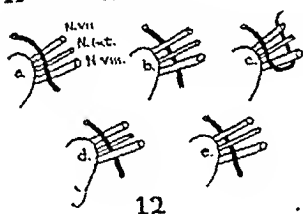


Fig. 11.—Eight positions relative to roots of facial, intermediate and acoustic nerves which may be assumed by internal auditory artery in its course to internal auditory meatus. Numerals indicate relative frequency of each position as noted in sixty-four cases.

Fig. 12.—Relation of anterior inferior cerebellar artery to roots of facial, intermediate and acoustic nerves. Artery may run ventral to (a), dorsal to (b) or in loop about (c) nerve roots; it may pass from ventral to dorsal surface between intermediate and acoustic nerves (d), or from dorsal to ventral surface in between intermediate and acoustic nerves (e).

Fig. 13.—Relations of anterior inferior cerebellar artery to root of abducens nerve. In a, artery lies ventral to nerve; in b, dorsal.

Fig. 14.—Relations of posterior inferior cerebellar artery to roots of glossopharyngeal, vagus and accessory nerves. Artery passes: in a, from a high origin to cerebellum ventral to nerve roots; in b, from a low origin in a loop ventral to nerve roots; in c, from a high origin superior to glossopharyngeal nerve, crossing it on way to cerebellum, and in d from a low origin, as a loop on way to cerebellum in concavity of which nerve roots are contained. In either of last two positions artery may press on ninth nerve and be in danger during operation on this nerve.

Just dorsal to the nerve root, and often as well somewhat lateral to it, is a vein which passes from the superior surface of the cerebellum to the superior petrosal sinus. This vein is in the direct route of the surgeon, and prevents perfectly free access to the root of the nerve.

Recently a case has come to our notice which ended fatally after section of the sensory root of the trigeminal nerve. At operation a sudden hemorrhage occurred immediately following the avulsion of the nerve root with a blunt hook. The bleeding was hard to control, but the wound was finally closed. Signs of increasing intracranial pressure gradually developed, and the patient died in the course of a few days, in spite of the remedial measures, which included a second operation revealing an extensive blood clot surrounding the medulla and pons.

The postmortem examination led to the conclusion that the main stem of the anterior inferior cerebellar artery had been torn, presumably because it possessed an unusually large loop which had allowed it to be picked up with the nerve. The main stem of the artery was filled with a solid clot and was separated from its origin on the basilar artery. The vessel was also embedded for some distance in the large clot which had formed at the base of the brain.

*Abducens Nerve.*—Section of this nerve is never indicated, since it is made up wholly of motor fibers. It lies very near the midline and is crossed by the main trunk of the anterior inferior cerebellar artery. In most cases this crossing lies close to the surface of the brain, but sometimes the artery is rather tortuous and forms a loop which extends farther out on the nerve. The artery may lie either dorsal to (figs. 4L and 8R) or ventral to (figs. 4R, 5 and 6) the nerve.

When the artery lies dorsal to the nerve it may exert pressure. Both Cushing<sup>2</sup> and Stopford<sup>1</sup> have suggested this as a cause of paralysis of the sixth nerve. In one case we found the nerve situated in a tight loop (fig. 9L) formed by the tortuous crossing of the anterior and the posterior inferior cerebellar artery just lateral to the nerve. Such a relation, it seems, might easily result as Stopford has suggested.

We observed that the dorsal position of the artery was encountered in twenty-four cases and the ventral position in forty-seven. These figures give a much higher proportion of cases with the artery in the dorsal position than those cited by Stopford, who noted this arrangement on the right side in 14 per cent of his cases and on the left in 19 per cent.

*Facial, Intermediate and Acoustic Nerves.*—Since the roots of these three nerves arise close to each other and all of them pass out together to enter the internal auditory meatus, their relations to the blood vessels are considered as a unit.

---

2. Cushing, Harvey: Strangulation of the Nervi Abducentes by Lateral Branches of the Basilar Arteries in Cases of Brain Tumours, *Brain* 33:204, 1910.

The artery which is constantly associated with this group of nerve roots is the internal auditory. The artery supplies not only the nerve roots but the sense organs of the internal ear, namely, the cochlea, the sacculæ, the utricle and the semicircular canals. It is therefore extremely important that the artery should not be wounded.

Its protection would be easily insured if it were as constant in position as one is led to believe from the descriptions in the various textbooks. It is described as coursing medially to the facial nerve and therefore in a safe location, since the only nerve section performed on this group of roots is that of the more lateral half of the acoustic nerve, which contains the fibers of the vestibular portion.

As a matter of fact, the internal auditory artery is extremely variable in its position, and in some of these locations it is in distinct danger. We have noted it passing in company with the nerve roots to the internal auditory meatus in eight distinct positions (fig. 11), which may be listed as follows:

#### A. Ventral positions

1. Medial to the facial nerve (figs. 3 *L*, 4 *R*, 6 *R*, 8 *L* and 10 *R*)
2. Between the facial and the intermediate nerve (figs. 5 *L* and 10 *L*)
3. Between the intermediate and the acoustic nerves (figs. 5 *R* and 8 *R*)
4. Lateral to the acoustic nerve (fig. 7 *R*)

#### B. Dorsal positions

5. Medial to the facial nerve (figs. 3 *R* and 6 *L*)
6. Between the facial and the intermediate nerve (figs. 9 *R* and 9 *L*)
7. Between the intermediate and the acoustic nerve (fig. 4 *L*)
8. Lateral to the acoustic nerve (figs. 3 *R* and 7 *L*)

It is to be noted that in the positions dorsolateral and ventrolateral to the acoustic nerve the artery lies directly on that part of the nerve which the surgeon wishes to cut. The artery is therefore placed in danger, and the difficulty of the operation considerably increased. In five of a total of sixty-four cases, the internal auditory artery was observed to be situated in such a position of danger (fig. 11).

We also found that in six of the cases the internal auditory artery was double (figs. 3 *R*, 8 *R* and 8 *L*). In these instances one vessel was usually related to the facial and the other to the acoustic nerve.

The origin of the internal auditory artery is of special interest. The textbooks describe this vessel as a separate and independent branch of the basilar artery (fig. 2). In Italy this seems to be the more common origin, as appears in the work of Cavatorti,<sup>3</sup> who found that the artery arose in this manner on the right side in 70 per cent of his cases and on the left in 67 per cent. Working in two such widely separated regions

3. Cavatorti, P.: Il tipo normale e le variazioni delle arterie della base dell'encefalo nell'uomo, *Monitore zool. ital.* 19:248, 1908; abstr., *Jahresb. u. d. Fortschr. d. Anat. u. Entwicklungsgesch.* 14:296, 1908.



as England and Japan, however, Stopford<sup>1</sup> and Adachi<sup>4</sup> noted independently that in the great majority of cases the internal auditory artery is a branch of the anterior inferior cerebellar artery and is given off as the latter vessel crosses the region of origin of the facial and of the acoustic nerve. In this investigation we found only three cases in which the internal auditory artery arose independently from the basilar (fig. 3*L*). In all of the other cases it was a branch of the anterior inferior cerebellar artery (figs. 3 to 10).

We also noted that the main trunk of the anterior inferior cerebellar artery was in constant relation to the roots of the facial, the intermediate and the acoustic nerve. The artery is a branch of the basilar artery; it courses over the pons and passes the roots of the three nerves just mentioned to gain the under surface of the cerebellum. The vessel may lie in contact with either the dorsal (figs. 3*R* and 9*R*) or the ventral (figs. 4, 5, 6*R*, 7*R* and 10*R*) surface of the nerves; it gives off the internal auditory artery in one of the positions previously listed in the description of that vessel.

The anterior inferior cerebellar artery usually lies close to the surface of the brain and so does not interfere with the operation of dividing the vestibular part of the acoustic nerve. This is not always true, however, since the trunk of the artery sometimes lies far out from the brain on the nerve roots. Instances were seen also in which the artery rose in a loop (figs. 4*L* and 7*R*) some distance out on the nerve roots as it passed them. In a few cases the loop extended out far enough to come into contact with the petrous bone. In this position the vessel presents a distinct hazard, and, since it is of considerable size and supplies a large portion of the cerebellum, its injury, with the consequent application of ligatures or clips, is definitely to be avoided.

We have seen this vessel pass from the ventral to the dorsal surface of the nerves to which it is related by passing through the interval between the facial and the intermediate nerve (fig. 9*L*) or in a similar manner between the intermediate and the acoustic nerve (figs. 8 and 10*L*). Sometimes the passage is made in the reverse direction, that is, from the dorsal to the ventral surface through the same intervals (fig. 6*L*).

In the cases in which the anterior inferior cerebellar artery passes between the nerve roots of the intermediate and the acoustic nerve it is held firmly in position and is difficult to move aside. This passage is sometimes made far from the brain surface, close to the mouth of the internal auditory meatus, and thus in the region in which the surgeon divides the vestibular nerve.

---

4. Adachi, B.: *Das Arteriensystem der Japaner*, Kyoto, 1928, vol. 1, p. 119.

In conversation with Dr. Kenneth G. McKenzie, we learned that he has met cases similar to those cited and that they were a source of bewilderment, since he could find in the textbooks no mention of a large vessel the position of which corresponded to that seen at operation.

*Glossopharyngeal, Vagus and Accessory Nerves.*—These three nerves arise from an almost continuous series of rootlets emerging from the anterolateral surface of the medulla oblongata. After the addition of the spinal root to the accessory nerve, the nerves pass through the jugular foramen. The glossopharyngeal nerve lies anteromedial to the others and passes separately through the dura mater.

Only on the glossopharyngeal nerve, which he divides close to the jugular foramen, does the surgeon operate intracranially for the relief of such conditions as tic douloureux. The vessels, therefore, the relationships of which are of practical interest here are those connected with the ninth or glossopharyngeal nerve.

The posterior inferior cerebellar artery chiefly holds this relation. It arises in the great majority of cases from the vertebral artery (figs. 7, 8 and 10), but sometimes from the basilar (figs. 3 R, 4 L, 6 R and 9 R). It often forms a loop with the convexity forward (figs. 5, 7 R, 8 L and 9 L), and it comes in contact with the ventral surface of the rootlets of the glossopharyngeal, vagus and accessory nerves on its return to the under surface of the cerebellum. It usually lies close to the medulla, and frequently fails to extend as far forward as the glossopharyngeal nerve. In all such instances the vessel is not in danger. The textbooks state that it passes through the interval between the vagus and the accessory nerve to reach the cerebellum (fig. 4 L). In only three of the fifteen cases in which the artery occurred in the ventral position did we have the vessel passing through the interval between these nerves. In no case did the artery pass through the interval between the glossopharyngeal and the vagus nerve.

Other cases were noted, however, in which the artery arose farther forward than usual (fig. 9 L) or the loop extended well forward (fig. 7 R), so that the vessel extended farther laterally under the nerve and might therefore be cut in section of the latter.

A position invoking a greater hazard is that in which the artery arises high on the vertebral or occasionally on the basilar artery and crosses superiorly (or dorsally) to the nerve on its way to the cerebellum (figs. 6 R and 8 R). Viewed from above, the nerve and the artery appear in crossing each other to form a figure like the letter X, with the vessel superior and therefore in considerable danger in cases in which the glossopharyngeal nerve is to be divided.

The position of greatest danger to the vessel is one seen occasionally (figs. 6 L and 10 L) in which the posterior inferior cerebellar artery arises from the vertebral artery ventral to the nerve roots and then

runs superiorly to form a loop about the glossopharyngeal nerve. The artery then passes in the opposite direction to course on the surface of the cerebellum. The glossopharyngeal nerve is thus contained within the concavity of a loop formed by the artery. The vagus and the accessory nerve also, of course, lie within this loop. With the artery arching over the nerve in this fashion, access to the nerve for the purpose of cutting it is rather difficult. Pressure of an arterial loop such as that just described on the ninth nerve may well be the cause of severe glossopharyngeal neuralgia, as surgeons have suggested.

*Hypoglossal Nerve.*—This nerve is purely motor, and therefore intracranial section is not indicated. In this location it is also rather difficult of access. The vertebral artery lies inferior and anteromedial to the origin of the nerve. The posterior inferior cerebellar artery may course anterior to (on the ventral surface of) the nerve if the vessel arises high on the vertebral artery. This is of no practical significance.

*Comment.*—In conclusion, we wish to emphasize the extreme variability both of the origin and of the course of the arteries in the posterior cranial fossa. The descriptions of these vessels found in standard textbooks of anatomy are wholly inadequate and of little aid to the surgeon in providing definite, detailed information on which to base his surgical technic. We are at present preparing a full anatomic description of the vessels in the region which we have studied; this is to be published later.

#### SUMMARY

Those arteries of the posterior cranial fossa which have definite relations to the nerve roots have been described.

Emphasis has been laid on the practical application of these relations to operations on the nerve roots.

An almost constant branch of the basilar artery runs laterally across the pons to pass out on the ventral surface of the sensory root of the trigeminal nerve. The term "trigeminal artery" is suggested for this vessel.

The main trunk of the anterior inferior cerebellar artery shows many and varied relations to the roots of the facial, intermediate and acoustic nerves. It lies either dorsal to or ventral to the nerve roots; it may loop around them or may pass between any two of them.

In the vast majority of cases the internal auditory artery arises from the anterior inferior cerebellar artery and not from the basilar artery, as is stated in the textbooks.

The internal auditory artery may occupy many positions as it emerges with the nerves. It may be either dorsal or ventral to them, between any two of them, medial to the facial nerve or lateral to the acoustic nerve.

The posterior inferior cerebellar artery is in relation to the glossopharyngeal, the vagus and the accessory nerve. It may be ventral or dorsal to them, cross superiorly to the glossopharyngeal nerve or form a loop over that nerve. It may pass between the vagus and the accessory nerve.

Diagrams illustrating all of the positions already mentioned are included.

In the series of cases which we have reviewed, nearly all of the possible positions of the arteries were noted, and we have elaborated on them with special reference to their relations to the nerve roots and to the practical application of this knowledge by the surgeon.

# ACUTE APPENDICITIS IN CHILDREN

CALEB S. STONE JR., M.D.

SANTA BARBARA, CALIF.

The diagnosis of acute appendicitis in children is frequently difficult because of the handicaps encountered in obtaining an accurate history and in performing an adequate physical examination. These difficulties may lead to the impression that there is a fundamental difference in the disease in children and in adults. The problem has been analyzed with reference to incidence, bacteriology, etiology, symptomatology, subjective and objective signs, mortality and factors influencing mortality in children in order to determine any differences there may be in the manifestations of acute appendicitis in children and in adults.

The records of 258 patients under 15 years of age admitted to the University of Virginia Hospital from 1925 to 1932, inclusive, which were filed under the diagnosis of "acute appendicitis" were reviewed. For purposes of comparison, certain figures have been drawn from a statistical study of the series of cases of acute appendicitis in adults, seen in this clinic during the same period.

## INCIDENCE

The age, race and sex distribution for this series of cases are shown in table 1. No cases were encountered in children under 2 years of age. This emphasizes the fact that this condition is rare in infants. Abt,<sup>1</sup> in 1917, was able to find reports of only 80 cases of acute appendicitis in children under 2 years of age.

The incidence in this series rose gradually between the third and twelfth years. After this time there was a marked increase in the number of cases, the incidence in each of the last three years (thirteenth to fifteenth, inclusive) being fairly constant. In a series of 208 cases of acute appendicitis in children under 14 years of age studied by Richter,<sup>2</sup> the peak of the age distribution curve was noted in the tenth year, and there was a decided decline in the incidence in the succeeding

---

From the Department of Surgery and Gynecology, University of Virginia School of Medicine.

1. Abt, I. A.: Appendicitis in Infants, *Arch. Pediat.* 34:641 (Sept.) 1917.

2. Richter, H. M., in Abt, Isaac A.: *Pediatrics*, Philadelphia, W. B. Saunders Company, 1924, vol. 3, p. 560.

years. In the series of cases from the St. Louis Children's Hospital (325 cases) reported by Keyes,<sup>3</sup> the peak was reached at the twelfth year, and was succeeded by a gradual decrease. The age distribution in these three series of cases suggests that in a large series the increase in incidence would be gradual, with no sharp rise at any age period during childhood.

In the present series of 258 cases, 55 per cent were in boys and 45 per cent in girls. This difference is not significant in this relatively small series, yet it is suggestive of the greater incidence in boys reported by other observers,<sup>4</sup> and of the greater incidence in men.<sup>5</sup>

TABLE 1.—*Distribution of Cases According to Age, Race and Sex*

Age	White		Negro		Total		Deaths
	Boys	Girls	Boys	Girls	Boys	Girls	
1.....	0	0	0	0	0	0	0
2.....	3	3	0	0	3	3	1
3.....	3	3	0	1	3	4	0
4.....	2	1	0	0	2	1	0
5.....	6	3	0	1	6	4	1
6.....	8	4	1	0	9	4	1
7.....	10	4	0	0	10	4	2
8.....	10	5	1	0	11	5	1
9.....	8	6	3	4	11	10	1
10.....	8	9	2	1	10	10	4
11.....	10	6	5	0	15	6	2
12.....	11	26	3	6	14	32	3
13.....	18	13	3	3	21	16	2
14.....	23	16	4	1	27	17	2
Total.....	120	99	22	17	142	116	20
Per cent.....					55	45	

In this series there were 219 white and 39 Negro children. These figures probably do not indicate the true ratio of acute appendicitis in white and in Negro children, though they approximate those given by Maes, Boyce and McFetridge.<sup>4c</sup>

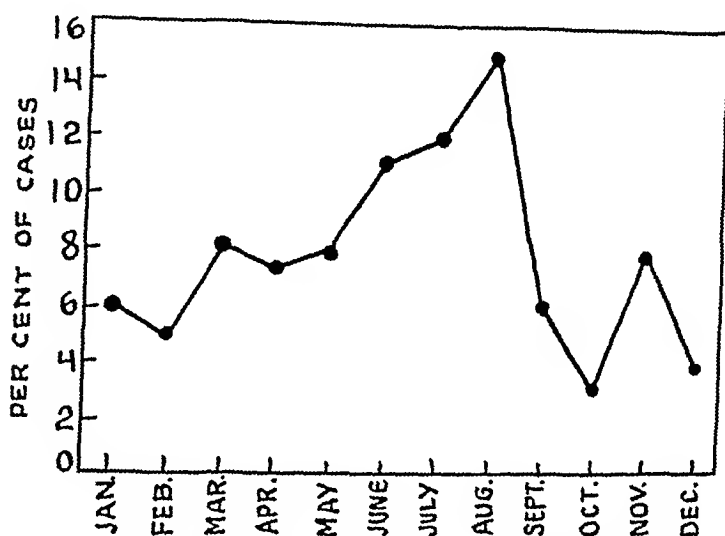
The seasonal incidence is shown in table 2 and in the chart. It is interesting that the peak of the curve of incidence of acute appendicitis comes in June, July and August. That the greatest incidence occurs

3. Keyes, E. L.: Death from Appendicitis, *Ann. Surg.* 99:47 (Jan.) 1934.

4. (a) Richter.<sup>2</sup> (b) Alexander, E. G., and Deaver, J. B., quoted by Richter.<sup>2</sup> (c) Maes, U.; Boyce, F. F., and McFetridge, E. M.: Acute Appendicitis in Childhood, with a Critical Analysis of 250 Cases, *Surg., Gynec. & Obst.* 58:32 (Jan.) 1934.

5. Keyes, E. L.: Death from Appendicitis, *Ann. Surg.* 99:47 (Jan.) 1934. Finney, J. M. T., Jr.: Appendicitis, *Surg., Gynec. & Obst.* 61:360 (Feb.) 1933.

in those months when intestinal infections are most common suggests a close relationship between such conditions and acute appendicitis. The absence of an increase in the number of cases of appendicitis during the spring and fall may indicate that infections of the respiratory tract are of little etiologic significance.



Seasonal incidence in 258 cases of appendicitis.

TABLE 2.—Distribution of Cases by Months and Years

	Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Total
1925.....	1	0	2	1	4	4	4	4	5	1	2	2	30
1926.....	1	0	1	2	3	6	1	5	3	1	4	3	36
1927.....	0	1	3	3	1	5	3	5	4	0	1	0	26
1928.....	5	3	3	1	3	5	5	7	1	0	2	0	35
1929.....	2	1	4	6	2	2	3	6	1	1	5	1	34
1930.....	3	1	5	2	3	2	7	2	2	2	4	3	36
1931.....	0	1	3	2	1	2	6	5	2	1	2	1	26
1932.....	4	1	2	4	5	4	4	5	1	3	1	1	35
Total...	16	14	23	21	22	30	33	39	19	9	21	11	258
Per cent	6.1	5.4	8.9	8.1	8.5	11.6	12.7	15.1	7.3	3.4	8.1	4.1	99.3

#### ETIOLOGY

*Bacteriology.*—Appendicitis is an acute infectious disease which may be caused by a variety of organisms. Bacteriologic studies were made in only 42 cases in this series, the majority of cultures being obtained in cases of appendicitis with perforation. Pure culture of *Bacillus coli* was obtained in 26 cases. Scattered pure cultures of *B. aerogenes*, *Staphylococcus* and *Streptococcus* were obtained, and these organisms were also found mixed with *B. coli* in a few instances. In 9 cultures there was no growth. Although few of these cultures were made from

unperforated appendixes, the results closely approximate those reported by Warren,<sup>6</sup> who made cultures from various portions of the wall of the unruptured, acutely inflamed appendix—outside the mucous membrane. The majority of cultures showed *B. coli*.

Jennings<sup>7</sup> has drawn attention to the rôle of *Bacillus Welchii* in acute appendicitis and in peritonitis following perforation of the appendix. No anaerobic cultures were made in this series.

Many modifying factors have been suggested which have a bearing on the etiology of acute appendicitis. These may be classified as follows:

- Previous inflammation of the appendix
- Obstruction of the lumen
  - (a) Foreign bodies
  - (b) Worms
- Acute infectious disease
  - (a) Infection of upper respiratory tract
- Gastro-enteritis
- Dietary indiscretion
- Abdominal trauma

*Previous Inflammation of the Appendix.*—A definite history of one or more previous attacks of acute appendicitis was recorded in 62, or 24 per cent, of the cases in this series. There were no fatalities in this group. As will appear later (table 4) this series of cases has been classified under three heads, depending on the extent of the disease. Of these recurrent cases, 50 were in group 1 (acute uncomplicated appendicitis), 8 in group 2 (acute appendicitis, ruptured, with local peritonitis) and 6 in group 3 (acute appendicitis, with general peritonitis).

Seventy-eight per cent of this group, therefore, were operated on before the infection spread beyond the appendix, as compared to only about 55 per cent for the whole series. This suggests two possible factors influencing the course of the disease. In the first place, the fact that 3 patients recovered spontaneously from a previous attack and that the present attack was mild suggests a greater general resistance to infection, whatever that may mean. In the second place, it is entirely possible that many of the patients had been put on the alert by the previous trouble and had sought medical aid sooner.

*Obstruction of the Lumen.*—(a) Foreign Bodies: Fecaliths were the only foreign bodies found in this series, and were reported in 38 of 258 cases. It is probable that fecal concretions occurred more frequently than were recorded. Though it cannot be proved by this study that the impaction of a fecalith actually precipitated the attack of acute

6. Warren, Shields: The Etiology of Acute Appendicitis, *Am. J. Path.* 1:241 (March) 1925.

7. Jennings, J. E.: The Relationship of the Welch Bacillus to Appendicitis and Its Complications, *Ann. Surg.* 93:828 (April) 1931.



appendicitis, the operative note in many instances suggests that the fecalith was a factor in the rupture of the appendix. It is striking that fecaliths were found in the three appendixes that ruptured in less than twenty-four hours after the onset of symptoms. This finding is in accord with the observations of Wilkie<sup>8</sup> on the importance of obstruction of the lumen by fecal concretion in the etiology of acute appendicitis.

(b) Worms: In 1913, 20.5 per cent of the children in a selected community served by this hospital were found to be infested with *Ascaris lumbricoides*.<sup>9</sup> Although this incidence has been greatly reduced, infestation is still fairly common. Despite the finding of *Ascaris* ova and worms in the stool and at operation in the intestine in a number of cases, no worms were found in the appendix in this series. Infestation with *Oxyuris vermicularis* is much less common in this district. However, in one instance these parasites were found within the lumen of the appendix. Although infestation with intestinal parasites is probably more frequent in children than in adults, from this study it appears to be a rare cause of acute appendicitis. Corroboration is found in the work of Suzuki<sup>10</sup> and of Gordon.<sup>11</sup>

*Infectious Disease.*—Acute tonsillitis immediately preceded the onset of acute appendicitis in 10 cases; in 2 cases the appendicitis quickly followed acute bronchitis, and acute appendicitis developed in 1 patient who was already in the hospital because of empyema of the pleura. In no other case in this group did appendicitis develop after a recognized preexisting condition.

Rosenow<sup>12</sup> presented evidence to indicate that appendicitis may be of hematogenous origin. On the other hand, Warren<sup>6</sup> was unable to confirm this idea. If there is any connection between infections of the throat and appendicitis, acute tonsillitis should be of more etiologic significance in children than in adults.

*Gastro-Enteritis.*—Attention has already been drawn to the higher incidence of acute appendicitis in children during those months when gastro-intestinal disorders are most frequent. Gastro-enteritis may be of etiologic significance, though no data are available from this study to confirm or to disprove this impression. Every surgeon has had experience with acute appendicitis following close on the heels of what

8. Wilkie, D. P. D.: The Etiology of Acute Appendicular Disease, *Canad. M. A. J.* **22**:314 (March) 1930.

9. Ann. Rep. Dept. Health Virginia, 1914, p. 98.

10. Suzuki, K.: The Rôle of *Oxyuris Vermicularis* in the Etiology of Appendicitis and Allied Pathological Conditions, *Surg., Gynec. & Obst.* **21**:702, 1915.

11. Gordon, H.: Appendiceal Oxyuriasis, *Ann. Int. Med.* **4**:1521 (June) 1931.

12. Rosenow, E. C.: The Bacteriology of Appendicitis and Its Production by Intravenous Injection of Streptococci and Colon Bacilli, *J. Infect. Dis.* **16**:240, 1915.

could be diagnosed only as gastro-enteritis, whether or not any infectious agent was shown.

*Dietary Indiscretion.*—Two patients in this group suffered an attack of acute appendicitis directly after overeating. Richter<sup>2</sup> mentioned 3 cases in a series of 172 in which dietary indiscretion was stressed in the history as initiating the attack. Since unwise eating, both as to amount and as to choice of food, is so common in children, it seems that if it were of etiologic significance such a history should be obtained more frequently.

*Abdominal Trauma.*—One patient in this group gave a history of having struck the lower portion of the abdomen on the corner of a table just prior to the onset of symptoms of appendicitis. The fact that no other patient gave a history of trauma suggests that this is rarely if ever a cause of appendicitis.

TABLE 3.—*Distribution of Pain at Onset and Frequency of Nausea and Vomiting*

Initial Symptom	Location of Pain at Onset	Number of Cases	Per Cent	Number of Cases in Which There Was	
				Nausea	Vomiting
Pain	Epigastrium.....	91	37.0	83	81
Pain	Right lower quadrant of abdomen.....	56	22.5	43	37
Pain	General over the abdomen.....	50	20.4	43	42
Pain	Lower portion of abdomen and about umbilicus.....	36	14.6	32	32
Pain	Left lower quadrant.....	4	1.6	3	2
Nausea and vomiting	.....	8	3.2	8	8
Total	.....	245	99.6	212	202
Not recorded in history.....	.....	13			

#### SYMPTOMATOLOGY

The usual sequence of symptoms, namely, pain somewhere in the abdomen, followed by nausea and vomiting and localization of pain in the right lower quadrant, is so constant in acute appendicitis that it is generally accepted as the rule. Pain was the first symptom in 237, or 96.7 per cent, of the 245 cases in which the history was adequate. The location of pain at the onset is shown in table 3. That only 37 per cent of these children complained of epigastric pain at the onset is in striking contrast with the usual textbook picture of acute appendicitis.

Nausea occurred in 212 of these cases, or 86.5 per cent, and was followed by vomiting in 202, or 82.4 per cent. Nausea with vomiting was given as the initial symptom in 8 cases. The high frequency of nausea and vomiting may be due to the fact that children are prone to vomit.

Localization of pain at McBurney's point occurred in 94.6 per cent of the 149 cases in which an adequate history was given. Localization

of pain occurred in from one to twelve hours in 36.1 per cent of these cases; in from twelve to twenty-four hours in 42.4 per cent; in from twenty-four to forty-eight hours in 17 per cent, and in from two to four days in 4.9 per cent.

#### SIGNS

Tenderness over McBurney's point was present in all but 1 of 247 cases in which the preoperative physical findings were properly recorded. The 1 exception was the case of a 12 year old child, who had been sick twenty-four hours before admission. At the onset of illness, there was epigastric pain, followed by nausea and vomiting and localization of pain in the right lower quadrant. On examination, a deep-seated mass was felt low on the right, but there was no tenderness or muscle spasm. At operation an acutely inflamed appendix was found, wrapped in omentum, lying deep in the iliac fossa. The obvious explanation for this exception is the lack of peritoneal involvement.

Tenderness with spasm of the right rectus muscle was present in 78.9 per cent of the cases. In a few cases in which the appendix was retrocecal, these findings were present in the right flank. A tender mass in the right lower quadrant of the abdomen was the principal physical finding in 6 per cent of the cases.

#### LABORATORY DATA

The laboratory test of most importance is the white blood cell count. The preoperative white cell count was recorded in 234 cases. In the 127 cases in which the appendix had not ruptured, the counts ranged from 6,000 to 29,000 (average, 15,200). Eighteen counts were under 10,000. In 70 cases in which a ruptured appendix was associated with localized peritonitis, the counts ranged from 6,400 to 33,600 (average, 18,700) and only 3 counts were under 10,000. In the 37 cases in which the peritonitis was not localized the counts ranged from 5,000 to 30,000 (average, 19,000), and 3 were under 10,000. Preoperative differential counts, Schilling counts and determinations of the sedimentation rate were done so rarely in the acute cases that analysis of the scattered results is not worth while. Chamber differential counts were reported preoperatively in most of the histories, but these, although clinically useful, are not adequate for a statistical study.

#### MORTALITY

To facilitate analysis of this series from the point of view of mortality, the cases have been arbitrarily placed in three groups as shown in table 4. A series of cases in adults seen in this hospital has been similarly divided in order to compare the distribution of cases and the mortality in each group. In those cases in children in which the appen-

dix was not ruptured there were no deaths. However, peritoneal involvement is followed by a relatively high mortality. The mortality is particularly high when there is a failure to localize the infection of the peritoneum.

Although the size of the adult series is much larger than that of the children, the distribution of cases in each of the three groups is so nearly the same that the mortality figures may be compared. The mortality in groups 1 and 2 of both series of cases is practically the same. In group 3 the mortality of 34 per cent in children as compared to 16 per cent in the adult is strongly indicative of a much lower resistance to peritoneal involvement in the child.

TABLE 4.—*Distribution of Cases and Mortality in Each Group*

Group	Distribution of Cases	Children				Adults			
		No. of Cases	Per Cent	Deaths	Per Cent	No. of Cases	Per Cent	Deaths	Per Cent
1	Cases of acute appendicitis, not ruptured.....	142	55	0	0	1,447	62	11	0.7
2	Cases of acute appendicitis, ruptured, with localization of peritonitis or definite abscess formation.....	72	25	5	6.9	552	24	20	4.3
3	Cases of acute appendicitis, ruptured, with no localization of peritonitis.....	44	17	15	34.0	337	14	39	16.0
Total.....		258	100	20	7.7	2,336	100	70	2.9

## FACTORS INFLUENCING MORTALITY

From these figures at least three factors that influence these mortality rates can be detected. The importance of early diagnosis and surgical intervention has already been demonstrated in table 4. In 116 (45 per cent) of the children in this series the appendix had ruptured before operation. There is good reason to believe from the histories that no appendix ruptured after admission to the hospital. Peritonitis developing after rupture of the appendix is the most serious complication to be considered in acute appendicitis in children.

The second factor seems to be the duration of illness before admission, which is closely related, of course, to the extent of the disease (table 5). Only 45 patients were admitted to the hospital in less than twenty-four hours after the onset of symptoms, which represents a small percentage of the entire series. Although the appendix was not ruptured in the majority of cases in which the patient was seen within the first forty-eight hours after the onset of symptoms, the 10 cases in which the appendix had ruptured in this interval emphasize the necessity of early removal.

A third factor in acute appendicitis is the use of cathartics (table 6). It is difficult to say whether or not catharsis will cause the rupture of an inflamed appendix or whether purgation after the rupture of an appendix will cause a spreading of the infection of the peritoneum. In 36 per cent of the histories in this series it was stated that one or more cathartics had been given prior to the patient's admission to the hospital. It is striking that there had been purgation in only 26 per cent of the cases in which the appendix did not rupture whereas it had been done in 47.5 per cent of those in which rupture occurred. The drugs most commonly used were castor oil, magnesium sulphate, mild mercurous chloride and "black draught" (an infusion of senna).

TABLE 5.—*Duration of Illness Before Admission*

Group	Duration of Illness Before Admission											
	0-12 Hours		12-24 Hours		24-48 Hours		48-72 Hours		After 72 Hours		Not Known	
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
1.....	17	0	25	0	43	0	27	0	27	0	3	0
2.....	0	0	0	0	4	0	12	0	55	5	1	0
3.....	0	0	3	0	3	1	15	5	23	9	0	0
Total	17	0	28	0	50	1	54	5	105	14	4	0

TABLE 6.—*Number of Patients Receiving Cathartics\**

Group	Patients Not Receiving a Cathartic			Patients Receiving a Cathartic		
	Number	Deaths	Per Cent	Number	Deaths	Per Cent
1.....	106	0	0	36	0	0
2.....	32	1	3.1	40	4	10.0
3.....	28	11	39.3	16	5	31.2
Total.....	166	12	7.2	92	9	9.8

\* Purgation was done in 47.5 per cent of the patients with a ruptured appendix and in 26 per cent of the patients with an unruptured appendix.

## COMMENT

The evidence presented indicates that there is no essential difference between the clinical picture of acute appendicitis in the child and that in the adult. An analysis of this series of cases indicates that the etiology, history and physical findings are identical for all practical purposes. The main difference lies in the higher mortality rate in children.

The difference in mortality in the two series of cases here reported is particularly striking in view of the fact that the distribution of cases in the three groups is practically the same in the two age periods.

There are several factors that may indirectly contribute to the higher death rate in children. The omentum in the child hangs at a higher level than that in the adult, and is therefore less efficient in the walling off of an inflammatory process in the lower portion of the abdomen. This

fact may in part explain the lower resistance of the child to peritoneal involvement and, indirectly, the higher mortality. It is assumed by many surgeons that the thinness of the wall of the appendix in the child may permit earlier peritoneal involvement. This assumption is not supported by this study, since there were a large number of cases of acute inflammation of the appendix of more than forty-eight hours' duration without peritoneal involvement, and the incidence of peritonitis in children and in adults in the present series was about the same.

Difficulties in arriving at an early diagnosis may contribute to the mortality by delaying operation until after the appendix has ruptured. In spite of the fact that typical symptoms are present in the majority of cases, it is often difficult to obtain a complete history in younger children.

The figures presented here demonstrate that the more common physical findings are present in children as in adults, in the vast majority of cases. According to accepted opinion, the position of the appendix with reference to the abdominal wall determines the location of tenderness on physical examination. The records of the present series offer no evidence to confirm or dispute this opinion. In the individual case other findings than those noted may be of great significance, i. e., tenderness along the lower border of the liver, maximal tenderness and spasm in the right flank and tenderness or a mass on rectal examination. It must be noted that in the vast majority of cases the findings on which to base a diagnosis may be elicited early in the course of the attack.

Unfortunately gastro-intestinal disorders, described by the parents as "biliousness," "stomach ache" or constipation, which yield so promptly to some home remedy, usually a cathartic, are so frequent in children that appendicitis is not considered until the disease is well advanced and the diagnosis obvious. The supposed frequency of constipation as an accompaniment of appendicitis doubtless may contribute to the free use of cathartics. It should be the attitude of every physician and parent that each case of abdominal pain is a potential case of appendicitis and should be watched carefully and closely, laxatives and sedatives being withheld, until a diagnosis can be reached. In those few atypical cases in which this may not be possible, early exploration would be far safer than the risk of peritonitis following the rupture of the appendix. It must be emphasized that the incidence of perforation of the appendix in the present series is practically no larger than that found in the adult series. The greater mortality in children is undoubtedly due to the lower resistance of the child to peritoneal involvement, and prevention of this complication is of first importance in the reduction of the mortality.

## SUMMARY

Two hundred and fifty-eight cases of acute appendicitis in children proved by operation have been reviewed. Certain outstanding findings have been emphasized. In this series the age distribution curve reached a peak at 12 years and remained high during the following two years. The results of this and similar studies indicate that there is a gradual increase in incidence from infancy to adult life, rather than a sharp increase at a given age period.

The greatest frequency of acute appendicitis in children was noted in the months of June, July and August. Since gastro-intestinal disorders are so common during the same period, such conditions may be of importance in the etiology of appendicitis.

A definite history of one or more previous attacks of acute appendicitis was noted in 64 of the cases in this series. The fact that 50 of the cases were in group 1 suggests greater resistance to infection and greater watchfulness on the part of the parents in subsequent attacks.

The general clinical picture of the disease in children was found to be similar to that in adults. Figures derived from this series of cases have been compared with figures drawn from a series of cases in adults seen in this clinic. The distribution of cases into three groups, namely, (1) acute appendicitis, not ruptured, (2) acute appendicitis, ruptured, with localization of peritonitis or definite abscess formation, and (3) acute appendicitis, ruptured, with no localization of peritonitis, was essentially the same in the two age periods. The mortality in groups 1 and 2 was essentially the same in the two series, but in group 3 the mortality in the children was 34 per cent as compared to 16 per cent in the adults. This high figure in group 3 in children accounts largely for the difference in total mortality, 7.75 per cent in children and 2.9 per cent in adults.

It appears from this study that the high mortality in children is due to the lower resistance to peritoneal involvement. It is obvious that reduction in mortality can best be accomplished by early diagnosis and removal of the appendix before involvement of the peritoneum occurs.

THERAPEUTIC USE OF CONCENTRATED STREPTO-  
COCCUS SERUM OF NEW YORK STATE  
DEPARTMENT OF HEALTH

IN INFECTED WOUNDS

ADELE E. SHEPLAR, M.D.

MARTHA JANE SPENCE, M.A.

AND

WARD J. MACNEAL, M.D.

NEW YORK

In our series of twenty-six patients treated with the concentrated streptococcus serum of the laboratory of the New York State Department of Health, there are thirteen with infections which would ordinarily be classed in the field of general surgery. In six, the infection began in the hand. In three patients, the lesion was apparently induced by pressure or by accidental laceration, and in four streptococcic infection appeared after surgical operation. Of the thirteen patients, eight survived and five died.

INFECTIONS OF THE HANDS

Streptococcic infection of the hand or its digits is rather frequent in physicians, nurses and laboratory personnel in hospitals. It is often trivial, but sometimes tragic, and there is good reason to believe that early neglect or unwise treatment in the early stage of the infection may sometimes contribute to the later unfortunate course. On the other hand, a fortunate outcome with early recovery does not of itself prove the efficacy of the treatment followed except for that particular case. In the present series we have six patients with such infection of the hand.

CASE 1.—M. E., a youth, aged 19, a volunteer worker in the pathologic laboratory, noticed a small irritated abrasion on the hypothenar eminence of the right palm about March 6, 1933. He applied iodine. In the next two days the region became swollen and tender and discharged a small amount of pus. A

---

This work was made possible by a grant from the Josiah Macy Jr. Foundation.

From the Department of Pathology and Bacteriology, New York Post-Graduate Medical School and Hospital, Columbia University.

The patients whose records are utilized in this paper were treated in the clinical services of the following physicians: Dr. R. F. Carter, Dr. T. H. Cherry, Dr. J. F. Erdmann, Dr. C. M. Gratz, Dr. C. G. Heyd, Dr. A. A. Levy, Dr. H. Lynch, Dr. J. J. Moorhead, Dr. H. H. Ritter and Dr. J. E. Sheehan.



culture showed hemolytic streptococci. An ampule of 20,000 units of the concentrated streptococcus serum was injected subcutaneously into both arms. On the following day there was marked swelling about the sites of injection of the serum with an urticarial eruption extending from the shoulder to the wrist on both arms. This disappeared after two days, and the original lesion healed promptly. The patient regards the infected abrasion as a trivial affair but retains a vivid and unpleasant recollection of the serum sickness.

CASE 2.—I. N., a student nurse, aged 20, had cellulitis of the left hand early in January. This was incised, and she was admitted to the hospital as a patient from January 6 to 10. After returning to duty for five days, she was again admitted to the hospital with a temperature of 102.6 F. On January 24 a large abscess in the left axilla and another on the right side of the neck were opened. The pus from these contained streptococci, although the original lesion of the hand contained both staphylococci and streptococci. After the drainage on January 24, the patient received 40,000 units of the concentrated streptococcus serum on January 25 and an equal amount on January 26. She was discharged on February 11. The result was highly satisfactory. Her abridged clinical chart has been presented elsewhere,<sup>1</sup> as this case was selected as an example of this group used in a previous paper.

CASE 3.—M. D., a graduate nurse, while attending a patient in whom an infection developed following an operation, acquired an inflammation about the nail of the right ring finger on Aug. 9, 1933. After a culture was taken, 0.5 cc. of asparagine staphylococcus bacteriophage was injected into the tissues of the distal phalanx on August 11. The finger was kept moist and warm as far as the patient's duties would permit. It was deemed unnecessary for her to give up her service, and she continued on active nursing duty. On the following day the culture showed hemolytic streptococci predominating, and the finger was still swollen and tender. After an intracutaneous test at 8:43 a. m., which revealed no hypersensitiveness to horse serum, a second dose of 0.5 cc. of the concentrated streptococcus serum was given subcutaneously at 9 a. m., and at 9:15 a. m. the remainder of the ampule was given intravenously, the total amount in the three doses being 20,000 units. Improvement was distinctly evident the next morning, and in two more days the finger appeared to be normal. The patient remained on duty regularly. There was no untoward reaction, nor was there any serum sickness.

CASE 4.—R. M., a physician, aged 38, had an inflammation of the index finger on his left hand, apparently due to infection acquired in performing an autopsy. After forty-eight hours, he appeared for duty on Monday morning, Jan. 9, 1933, with signs of a severe infection. The finger was quite swollen, and there were visible red lines extending up the forearm and a painful swelling in the axilla. He was at once admitted to the hospital and put to bed. Microscopic examination and cultures of the exudate from the finger taken on the preceding Saturday showed predominant staphylococci.

The abridged clinical record is shown in chart 1. On January 9 experimental staphylococcus antitoxin was given in three doses to insure desensitization, and 1 cc. of staphylococcus bacteriophage was injected subcutaneously into the left arm near the axilla. On the next day our concern seemed rather ridiculous, but on January 11 the pain and swelling in the axilla had increased, and therefore further injections of staphylococcus bacteriophage were given subcutaneously

---

1. MacNeal, W. J.: Specific Treatment of Septic Infections, Particularly with the Aid of Bacteriophages, *Am. J. M. Sc.* 187:623 (May) 1934.

near the axilla on January 11 and 12. On January 13 a circumscribed deep axillary abscess was recognized, and on the next day, under ethylene-oxygen anesthesia, this was conservatively opened, and the major portion of the nail of the index finger was cut away. Microscopic examination of the axillary pus revealed definite chains of cocci, and the cultures subsequently gave a pure growth of hemolytic streptococci. Without awaiting the result of this culture, the patient was at once treated for the streptococcus infection. A blood culture was taken, which remained sterile. Two ampules, 40,000 units, of the concentrated streptococcus serum were given subcutaneously, and this dose was repeated on January 15. A distressing general urticaria with moderate laryngeal edema appeared on the evening of January 16, disappearing in twenty-four hours. The patient was discharged on January 19 and returned to duty on January 23.

This is the fourth instance of cellulitis of the hand and axillary adenitis observed in our staff as a result of infection contracted at autopsies in a period of twenty-two years. In the other three the period of hospitalization was a matter of months, and the final fortunate outcome seemed for a time doubtful. This fourth case in the series is the first one in which specific bacteriotherapeutic measures were employed.

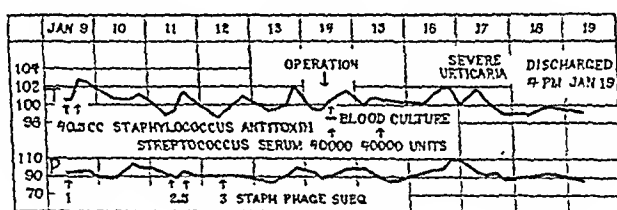


Chart 1.—Abridged clinical record of R. M., a man, aged 38. In this patient cellulitis of the left hand developed, apparently due to infection acquired in performing an autopsy. The patient was treated for infection with the staphylococcus until January 14, when incision of an axillary abscess revealed numerous streptococci. Streptococcus serum was given subcutaneously on January 14 and 15. Severe serum sickness developed on January 16. The patient was discharged on January 19 and returned to duty on January 23.

CASE 5.—M. R., a Negress, aged 46, employed in washing glassware in the laboratory, had an inflammation about the nail which developed after she pricked her right middle finger with a pin in the back of her apron on Feb. 18, 1933. On Sunday, February 19, the finger became increasingly painful and swollen. A slight fever, not accurately recorded, was present. On February 20 the finger was swollen for half its length, and the axillary nodes were enlarged. The swelling was most marked about the nail. This was punctured with a small sterile needle, and a small amount of blood-tinged pus was obtained. Microscopic examination revealed streptococci, and cultures gave colonies of hemolytic streptococci, *Staphylococcus albus* and colon bacilli of the aerogenic type. On February 20 a subcutaneous dose of 20,000 units of the concentrated streptococcus serum was given, and on February 25 the lesion on the finger was irrigated with coli bacteriophage. Progress was satisfactory. The patient was absent from duty only a half day, Monday afternoon, February 20. Her occupation, namely, washing laboratory glassware in warm water, may have contributed to the prompt recovery.

CASE 6.—J. H., a man, aged 46, received a puncture wound from a piece of wire beneath the nail of his right thumb on July 8, 1933. Several hours later the thumb became swollen and painful, and there were red streaks along the forearm, with soreness at the elbow and the axilla. On the day of admission to the hospital there had been several chills and a high fever. The patient came to the hospital at 6:30 p. m. on July 10. At this time the right thumb was swollen, and its distal third was yellow and without feeling. The entire hand was swollen, and there was a large prominence in the anterior interosseous region of the forearm. The right epitrochlear and axillary nodes were enlarged. The temperature was 106.2 F.

The abridged clinical record is shown in chart 2. Immediate operation revealed only a minute quantity of exudate at the tip of the thumb, but there was a large amount of pus at the thenar eminence. Gas bubbles were observed beneath the skin. Immediately after the operation there was a severe chill followed by a lowered temperature. Again on July 11 there was a chill lasting ten minutes. The patient began to cough and also to suffer from persistent attacks of hiccupping, which continued throughout most of his illness.

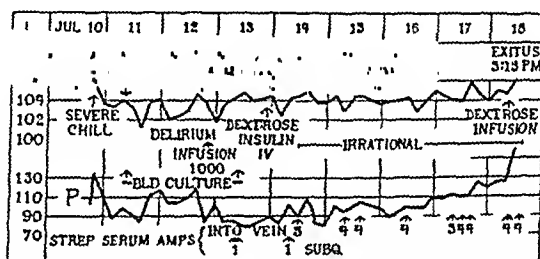


Chart 2.—Abridged clinical record of J. H., a man, aged 46. This patient had cellulitis of the hand and forearm following puncture of the right thumb. There was a mixed infection in which hemolytic streptococci were abundant. There were, however, also gas bubbles beneath the skin. *Streptococcus serum* was given on July 13, 14, 15, 16, 17 and 18, the total amount being 38 ampules, or 760,000 units. The forearm was incised on July 12, and the upper part of the arm was incised on July 15. The patient died on July 18. At autopsy, the streptococcus seemed to have played a minor rôle in the terminal stages of the disease.

Cultures of the pus obtained on July 10 yielded only hemolytic streptococci on the blood agar plates and in a test tube two-thirds full of dextrose meat infusion agar, and in litmus milk there was no evidence of growth of *Clostridium Welchii*. In blood broth, however, a slender gram-positive rod, evidently anaerobic, was found along with the streptococci and diphtheroid bacilli. Blood cultures taken on July 11 and 13 remained negative.

On July 12 the right arm was red and swollen to the axilla. At 5:30 p. m. on this day, multiple incisions were made in the forearm, and an abscess cavity was found above the annular ligament of the wrist and another in the upper third of the forearm. The patient was now delirious and remained irrational most of the time thereafter. He received several infusions of dextrose. On the evening of July 15, multiple incisions were made in the arm between the elbow and the axilla, and further incisions were made in the forearm. The cough became worse, and the patient raised mucus containing abundant small gram-negative rods, apparently Pfeiffer's bacilli.

The concentrated streptococcus serum was given first on July 13, one ampule of 20,000 units, in divided doses to insure desensitization. The same amount was given subcutaneously on July 14, and this was followed, after consultation with Dr. Maillard of the state laboratory, by massive intravenous doses, five ampules (100,000 units) at noon on July 14, eight ampules on July 15, four on July 16, eleven on July 17 and eight on July 18, the total serum given amounting to 38 ampules, or 760,000 units. The patient died on July 18.

Autopsy, performed five hours after death, disclosed purulent collections in the right elbow and shoulder joints, in addition to extensive dissecting purulent and emphysematous inflammation of the entire extremity, and bilateral lobular pneumonia. Pus from the shoulder joint yielded a few colonies of hemolytic streptococci; the predominant bacteria in cultures were green streptococci and diphtheroids. Anaerobic cultures yielded a slender gram-positive bacillus, not identified, and a few colonies of *Cl. Welchii*. Cultures of the heart's blood yielded only colonies of *Streptococcus viridans*. Apparently the activity of the hemolytic streptococcus in the mixed infection had been somewhat restricted by the serum but not completely suppressed.

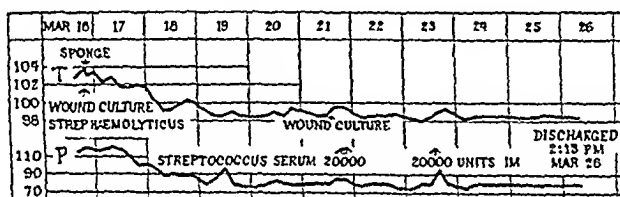


Chart 3.—Abridged clinical record of S. Y., a girl, aged 18. This patient had an accidental wound of the left cheek, which was heavily infected with streptococci. She received serum on March 21 and 23, with prompt local improvement.

#### ACCIDENTAL WOUNDS AND ULCERS DUE TO PRESSURE

In this subgroup there are three patients. One was the victim of an automobile accident, and the other two had infected ulcers caused by pressure. Two recovered and one died. None of them had a positive blood culture.

CASE 7.—S. Y., aged 18, the daughter of a physician, suffered a contused laceration of the left side of her face in a motor accident on March 14, 1933. A wound about 3 cm. in length was closed by eight sutures. Bleeding from the nose persisted for twenty-four hours, and on March 15 the temperature ranged from 102 to 103 F. She was admitted to the New York Post-Graduate Hospital on March 16, with marked swelling of the face and a temperature of 102.8 F. Two stitches were removed, and a drain was inserted in the wound. Culture taken at this time yielded abundant hemolytic streptococci. The abridged clinical record is shown in chart 3. On March 17 all the remaining stitches were removed. Drainage was abundant. Roentgenologic study revealed no evidence of fracture, but did reveal evidence of inflammation in the right antrum as well as of the soft tissues of the face. The condition was not considered dangerous, but the patient's father as well as the attending surgeon in the case requested the aid

of specific bacteriotherapy on March 21. After a culture was taken, which later showed hemolytic streptococci, the patient was given an ampule (20,000 units) of the concentrated streptococcus serum in divided doses to insure densitization on March 21, and the same amount was given in a single intramuscular injection on March 23. The drainage from the wound diminished promptly and ceased entirely on March 25. The patient was discharged on March 26 with a granulating wound in a satisfactory stage of healing.

CASE 8.—E. H., a woman, aged 37, had been under observation and treatment at the New York Post-Graduate Hospital for congenital dislocation and deformity of the left hip since Oct. 31, 1931. There had been three open surgical operations on the hip. The first two operations were performed in Europe in 1904 and 1921, respectively. After 1921 the patient had good function until March 1931, when she fell and hurt herself so that she was unable to walk for seven weeks. Again, about September 14, she fell and injured this hip and was

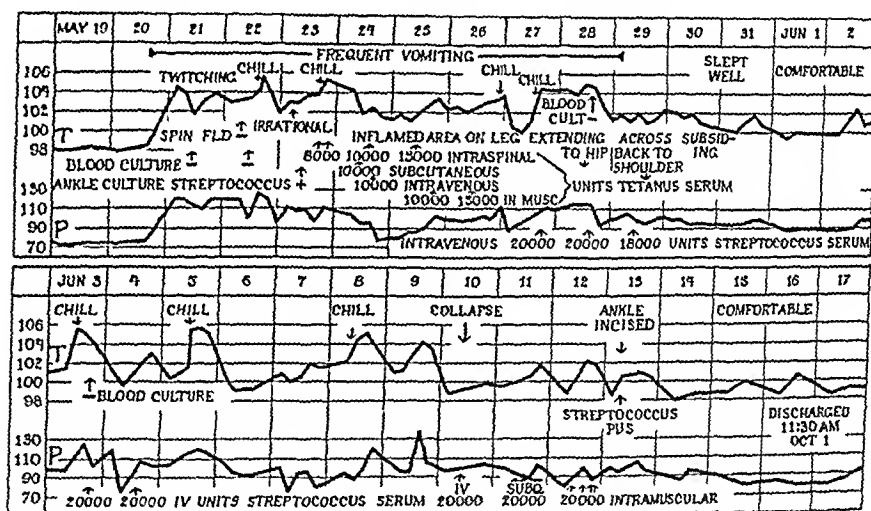


Chart 4.—Abridged clinical record of E. H., a woman, aged 37. Inflammation developed in the patient's leg, apparently due to pressure of a surgical dressing on May 20. A clinical diagnosis of tetanus led to the administration of tetanus serum, 33,000 units into the spinal canal, 10,000 units subcutaneously, 10,000 units intravenously and 25,000 units by intramuscular injection from May 24 to 26. An eruption diagnosed as erysipelas appeared on May 24. A blood culture remained negative. Streptococcus serum was given intravenously on May 27, 28 and 29, a total of 58,000 units. Prompt improvement followed this. On June 3, however, there was a chill, and streptococcus serum was given on this day and also on June 4, the total amount being 40,000 units. After an interval of five days a dose of 20,000 units of serum was given intravenously on June 10. A severe shock followed, evidently due to the serum. Divided subcutaneous doses were given on June 11, and divided intramuscular doses on June 12. The patient was discharged on October 1 in good condition.

not able to walk after that. The third operation at the New York Post-Graduate Hospital resulted in fixation by a bone graft, and following this the patient was discharged on Feb. 27, 1932, with a mechanical brace on the left lower extremity from the pelvis to the ankle. On March 9 the left ankle became swollen and

painful, and she noticed a small blister on it, which later became an ulcer. She came back to the hospital on March 13, and a course of light therapy, massage and electrical stimulation was instituted and continued to May 19. On the evening of May 20 the patient began vomiting and had a sharp rise in temperature and pulse rate.

Her abridged record after May 19 is shown in chart 4. She complained of severe pains in the hips, abdomen, back and head. Blood culture taken on May 21 remained negative, as did also subsequent blood cultures taken on May 22 and 28 and on June 3. On May 22 there was a chill lasting fifteen minutes, with stiffness of the neck, tremors of the mouth and jaw and arching of the back. Spinal tap yielded a normal spinal fluid. On May 23 the patient was irrational. Culture taken from the ulcer on the ankle showed hemolytic streptococci and *Staph. albus*. During the four days, from May 23 to 26, antitetanic serum, 33,000 units, was injected into the spinal canal, 10,000 units subcutaneously, 10,000 units intravenously and 25,000 units intramuscularly. Meanwhile the bacteriologic search for the tetanus bacillus by anaerobic culture methods and inoculation of animals gave negative results. The inflamed area on the ankle extended up the leg, reaching the region of the hip on May 28 and across the back to the level of the shoulder on May 29, after which it subsided. The concentrated streptococcus serum was given by intravenous injection, 20,000 units on May 27, the same dose on May 28 and 18,000 units on May 29. Clinical improvement was prompt. However, there was a chill and sharp rise in temperature on June 3; an intravenous dose of 20,000 units was given on this day and repeated on June 4. On June 8 there was increased pain in the left ankle and leg, and a chill with a rise in temperature to 105.2 F. On June 10 an intravenous injection of 20,000 units of the streptococcus serum was given, the interval after the previous dose having been six days. Two minutes later rigor and vomiting developed, and the pulse became imperceptible. Epinephrine was administered, and the collapse was relieved in about half an hour. On June 11 the same amount of serum was given in six subcutaneous doses without untoward effect, and on June 12 the same amount was given in four intramuscular injections without recognizable reaction. On June 13 the evidence of inflammation had disappeared except over the anterior aspect of the left ankle. This region was now incised and pus evacuated. Cultures of this pus yielded only hemolytic streptococci. Subsequent progress was satisfactory. The patient was kept under observation in the hospital until October 1.

CASE 9.—P. H., a man, aged 62, was admitted to the hospital on Feb. 16, 1933, with a painful ulcer on his left foot. In June 1929 he had a sore on the dorsal surface of his right great toe which healed after several weeks. The present ulcer on the other foot appeared about Jan. 12, 1933, and had gradually extended. Since February 2 the patient had been confined to bed. Mild diabetes had been recognized for ten years, and insulin had been used occasionally. The urine had usually been sugar-free in recent years.

The abridged clinical record is shown in chart 5. The ulcer was excised on February 16, and on February 18 the second and third metatarsal bones were opened and purulent osteomyelitis found. This operation was followed by a chill, but blood culture taken at this time remained negative. Culture from the wound revealed the hemolytic streptococcus, colon bacillus and staphylococcus. Bacteriophages active against the colon bacillus and against staphylococcus were applied to the wound; 30 cc. of staphylococcus antitoxin was given subcutaneously on February 19 and 1 cc. of staphylococcus bacteriophage intravenously. On this same day

40,000 units of the concentrated streptococcus serum was given subcutaneously in three doses. With continuation of this treatment the general condition improved so that the patient was allowed out of bed on February 22 and 23 and was able to act on some important papers sent in from his office. On February 24 an amputation was performed at the middle part of the left thigh, immediately following a transfusion of 340 cc. The patient did not rally from this operation.

#### INFECTED SURGICAL WOUNDS

In this subgroup there are four patients: a girl of 19 with staphylococcic osteomyelitis, secondarily infected with the hemolytic streptococcus; a man 30 years old with streptococcic infection following operation for inguinal hernia; a man 47 years old, in whom general sepsis developed after excision of the inguinal lymph nodes, and a woman of 60 years, who likewise suffered from general sepsis following operation on a proctocoele and hemorrhoids. Three died and one survived.

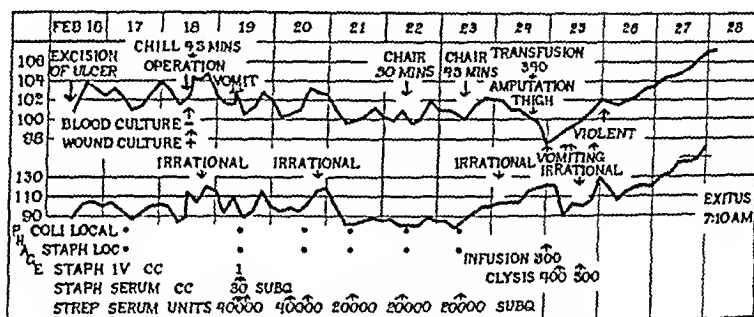


Chart 5.—Abridged clinical record of P. H., a man, aged 62. The patient had an ulcer on the dorsum of his left foot which extended to produce osteomyelitis of the metatarsal bones. Surgical excision and incision was supplemented by application of bacteriophage and the injection of streptococcus serum. A total of 140,000 units of streptococcus serum was given from February 19 to 23. The patient appeared somewhat improved. On February 24 the extremity was amputated in the region of the midthigh, after which the patient did badly and died on February 28.

CASE 10.—M. H., a school girl, aged 19, was admitted to the hospital on Jan. 19, 1933, with osteomyelitis of the right ilium which involved the hip joint and an infection of the blood stream with *Staph. aureus*. Her abridged clinical record has been presented in an earlier paper from this laboratory.<sup>1</sup> She survived about four months. During this time the septicemia was overcome, but the operative wound became secondarily infected with various organisms, among which the hemolytic streptococcus seemed for a time to be the most dangerous. Large doses of the concentrated streptococcus serum were given on two occasions with favorable effect on the streptococcic infection. However, the patient continued to lose weight and, after various complications, aspiration pneumonia developed, and death occurred on May 17, 1933.

CASE 11.—C. J. R., a man, aged 30, entered the hospital on Jan. 30, 1933, for relief of inguinal hernia which was ascribed to the effort of heavy lifting seven

weeks earlier. The abridged clinical record is shown in chart 6. A bilateral herniotomy was performed on January 31. The postoperative course was unsatisfactory, and on February 6 there was marked inflammation of the abdominal wall near the left incision, and pus was exuding from the incision. On February 7 the inflamed area was incised, and a culture of the exudate was taken. This yielded a growth of the hemolytic streptococcus. A transfusion was given on February 9 and, on the next day, multiple incisions were made in the abdominal wall. On February 14 the aid of bacteriotherapeutic measures was requested, and after a blood culture was taken, the concentrated streptococcus serum was administered, 20,000 units in three doses. The serum was continued on February 15, but after 5,000 units it was discontinued by order of the attending surgeon, who preferred to place his faith in other measures. A transfusion of 600 cc. was given on February 16. On February 17 the left seventh rib was resected, and the pleural cavity was opened. A small amount of sterile watery fluid containing cholesterol crystals was obtained. A blood culture taken on February 18 gave

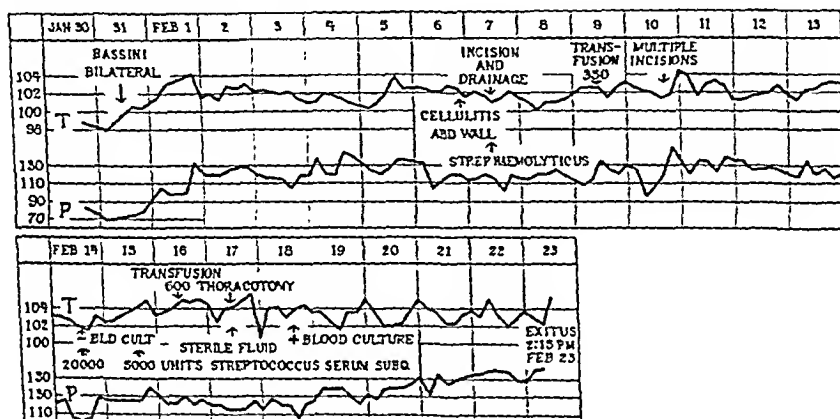


Chart 6.—Abridged clinical record of C. J. R., a man, aged 30. The patient was operated on for relief of bilateral inguinal hernia on January 31. Post-operative inflammation due to hemolytic streptococci was recognized on February 6. This was treated by transfusion and by multiple incisions. Streptococcus serum was started on February 14 and discontinued on February 15 after 25,000 units had been given. Transfusion of 600 cc. was performed on February 16, and a rib resection was done on February 17. On the next day a positive blood culture was obtained, the organism being a hemolytic streptococcus. The patient died on February 23.

a positive growth of hemolytic streptococci. On this day evidence of thrombophlebitis appeared in the left leg, and this condition progressed rapidly. The patient died on February 23.

CASE 12.—L. G., a man, aged 47, was admitted to the hospital on Feb. 20, 1932. In the latter part of January swellings developed in both inguinal regions, and on February 9 the patient's physician incised the right inguinal abscess and evacuated a quantity of pus. On admission to the hospital a draining sinus was present on this side, and there was inflammatory enlargement of the left inguinal nodes. On February 29 specimens were taken for biopsy from the right and left inguinal regions. These revealed a chronic purulent lymphadenitis without evidence of



tuberculosis. Pus taken at the same time from the right inguinal region failed to give any growth in dextrose broth and blood agar plates. These culture methods could hardly be expected to bring to development a possible bacillus of Ducrey but would seem adequate for the hemolytic streptococcus. The patient was discharged on March 8.

On May 14 he was again admitted to the hospital with continuing inguinal adenitis and a persistent small sinus in the right inguinal scar. The abridged clinical record from this date is shown in chart 7. On May 16 the old surgical scar in the right groin together with the underlying lymph nodes was excised. The microscopic study of this specimen disclosed a chronic purulent inflammation. Culture was not made. On May 18 the temperature rose to 104 F. Blood culture taken on May 20 revealed three colonies of hemolytic streptococci per cubic centimeter of blood. Clysis of 750 cc. on May 22 was followed by chill and a rise

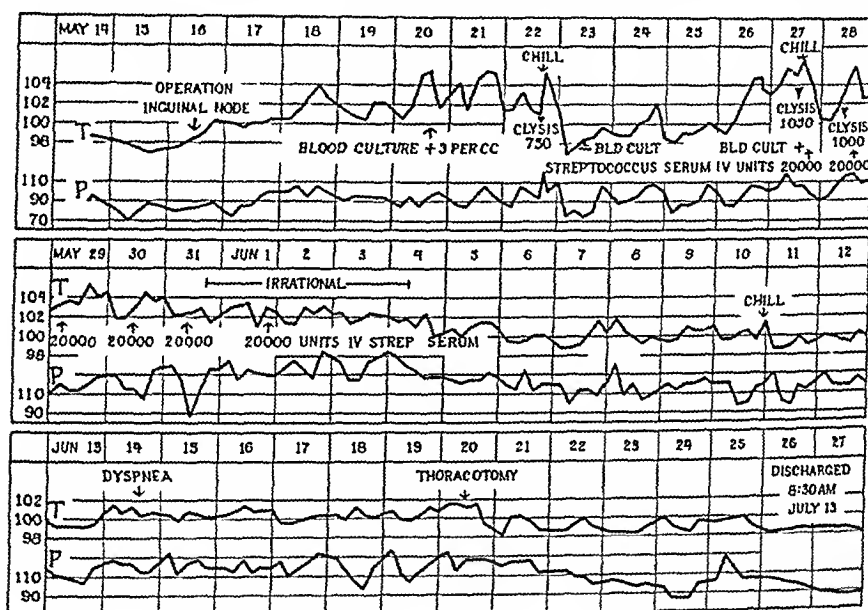


Chart 7.—Abridged clinical record of L. G., a man, aged 47. Bilateral inguinal adenopathy developed in January 1932, and a right inguinal abscess was incised on February 9. On May 16 a persistent sinus and the lymph nodes in the right inguinal region were excised. On May 20 blood culture yielded streptococci. Streptococcus serum was administered intravenously on May 27, 28, 29, 30 and 31 and June 1, a total of 120,000 units. The patient did well for a time, but on June 20 an exudate in the chest was evacuated by rib resection. He was discharged July 13 in good condition.

in temperature to 105.2 F. Blood culture taken on May 23, when the temperature was low, remained sterile. However, on May 27 a blood culture was taken which became positive for hemolytic streptococci. On this day the temperature reached 106.6 F. after a clysis of 10 per cent dextrose. At 6:30 p. m. the patient was given 20,000 units of the concentrated streptococcus serum intravenously, and this dose was repeated daily to June 1. Severe pain in the chest and labored breathing appeared on May 29, and on June 1 the cough raised some clotted blood as well as thick mucus. The patient was irrational much of the time from May 31 to June 4.

Therapeutic efforts, aside from the injections of serum, were discontinued after May 28. The patient gradually improved until June 10, when he complained of pain in the chest, and at night there was a chill lasting ten minutes. On June 15 there was dulness everywhere below the scapula on the right side of the thorax, and the signs of pleural exudate were confirmed by roentgenographic examination on June 18. On June 20, under local anesthesia, a thoracotomy evacuated pus under pressure occupying the entire right pleural cavity. Culture of the pus revealed abundant Pfeiffer bacilli and a few colonies of hemolytic streptococci. The postoperative course was satisfactory. The patient was allowed to be up in a chair on June 30; he walked on July 11, and was discharged with his wounds healed on July 13. There was no serum reaction in this case.

CASE 13.—S. H., a woman, aged 60, was admitted to the hospital on May 2, 1932. Her abridged clinical record is shown in chart 8. On May 4, under nitrogen monoxide and ether anesthesia, operations for internal hemorrhoids and for proctoceles were performed. On May 6 bleeding from the vaginal wound was con-

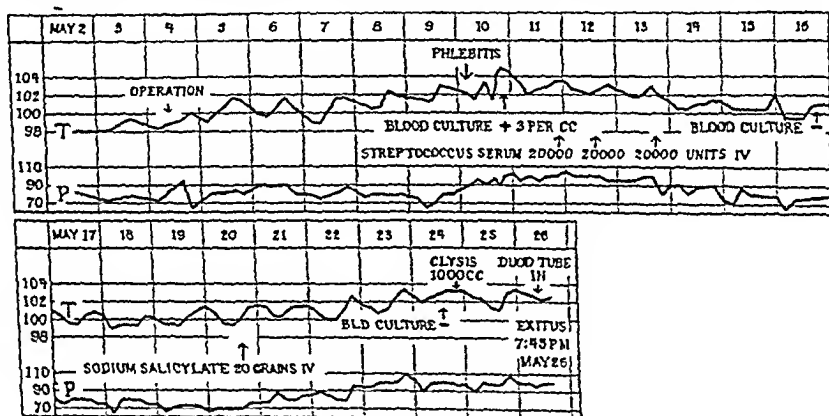


Chart 8.—Abridged clinical record of S. H., a woman, aged 60. This patient had a perineal operation and hemorrhoidectomy on May 4. On May 9 thrombophlebitis developed in the left thigh, and a positive blood culture was obtained on May 10. The serum was given intravenously on May 11, 12 and 13, a total of 60,000 units, followed by marked improvement. However, the condition became worse again on May 19. Sodium salicylate was given intravenously on May 20. The patient died on May 26.

trolled by packing. The temperature continued to mount gradually. On the night of May 9 severe pain developed along the inner side of the left thigh, and by morning of May 10 there was definite tenderness along the femoral vein. The temperature rose to 105 F., and petechiae appeared over the body. A blood culture taken that evening yielded three colonies of hemolytic streptococci per cubic centimeter of blood. The concentrated streptococcus serum was given intravenously, 20,000 units each on May 11, 12 and 13. The temperature response was satisfactory, and a blood culture taken on May 16, as well as one on May 24, was negative. However, on May 13 the urine showed some protein (one plus) and a considerable number of leukocytes as well as granular casts. Culture of the urine was not undertaken. On May 20 there was moderate vaginal bleeding, and there was edema of the left buttock and an inflamed area in the left inguinal region.

An intravenous dose of 20 grains (1.3 Gm.) of sodium salicylate was given on this day. On the next day the area of inflammation had extended, and the patient became mentally confused. Vaginal bleeding continued. There was no evidence of serum disease. The patient died on May 26. Postmortem examination was not permitted.

#### COMMENT

In these thirteen patients making up a somewhat heterogeneous group there were eight survivors and five who died. Six of the patients had infections of the hand, the impending gravity of which cannot be accurately estimated in advance. The lesions when first seen were of such a nature that surgical incision for drainage would have been the treatment of choice in our hospital only a few years ago. Three of these patients were treated without incision by bacteriotherapeutic measures in which the concentrated antistreptococcus serum of the laboratory of the New York State Department of Health was evidently the important factor. Warmth and moisture were employed locally. In these three the threatening disorder proved to be trivial. In two of the patients, a nurse, I. N., and a physician, R. M., the serum was given only after surgical incision of an axillary abscess which revealed the streptococcus. The recovery was surprisingly prompt in both. The sixth patient of this group, J. H., obviously had a mixed infection in which anaerobic bacteria as well as streptococci were concerned. His thumb and hand were incised on July 10, and on July 12, multiple incisions were made in the wrist and forearm; again on July 15, multiple incisions were made in the forearm and in the upper part of the arm. The serum was first given on July 13, and it was increased to a total amount of 760,000 units without success. However, at the autopsy it appeared that the dangerous hemolytic streptococcus, so abundant in the original wound, had not played the important rôle in the fatal outcome.

As a result of our experience we have become somewhat more conservative in the matter of incising infected fingers. Exudate is needed for microscopic examination and culture, but when these examinations are inconclusive or even while their outcome is being awaited, we favor the use of prophylactic bacteriotherapeutic measures and especially the streptococcus serum. We do not wish to suggest that surgical incision of infected fingers and hands should never be undertaken, but we do believe that the early use of serum against streptococcic infection will often suffice to limit the extension of the disease and to avoid serious deformity. It is perhaps not too much to hope that the disabling scar contractures, the long weeks of hospitalization and the occasional tragic fatality following streptococcic infection of the hands, especially in physicians and nurses, may be ameliorated by the early administration of a potent antistreptococcus serum. Even when incisions are made, we are convinced that the streptococcus serum, as exemplified by the

concentrated serum of the New York State Department of Health, offers an important aid in further combat against the infection.

In the one patient with a recently inflicted gash in the face resulting from a motor accident, a threatening streptococcic infection rapidly subsided after the administration of the serum, a matter of some importance in relation to scar formation, particularly on the face of a young woman.

The two patients with ulceration on the lower extremity responded favorably to treatment with the streptococcus serum. In one of these, E. H., there is an emphatic illustration of the danger sometimes encountered in giving horse serum intravenously. This patient received the concentrated streptococcus serum on May 27 and 29 and on June 3 and 4. Then after an interval of six days she received an intravenous injection of 20,000 units of the same serum. Severe shock appeared in two minutes, and the alarming condition persisted for half an hour. We have had opportunity to observe similar reactions of hypersensitivity, so far without a fatal result, in several other patients, particularly when there has been a considerable interval between the successive doses of this serum, and we therefore urge extreme care in desensitization in all such cases. The outcome in this particular patient was fortunate. Without the serum she would probably have succumbed. The other patient, P. H., with ulcer of the foot, responded well to the bacteriotherapeutic measures, which were then discontinued in favor of a radical operative procedure with unfortunate outcome.

In the group of four patients with postoperative infections, the streptococcus serum accomplished, in our opinion, all that could reasonably have been expected of it. In M. H. the serum was resorted to with success on two occasions when a progressive streptococcic infection seemed otherwise uncontrollable. The eventual death of the patient took place without recognizable activity of the hemolytic streptococcus. The second patient, C. J. R., with extensive cellulitis of the abdominal wall, received only 25,000 units of the serum. Three days later, after a thoracotomy, the streptococcus had invaded the blood stream and the process became progressively worse until death on February 23, further serum treatment not being permitted. The third patient, L. G., affords an excellent contrast. After two positive blood cultures and a rise in temperature to 106.6 F. on May 27, this patient was given 120,000 units of the serum intravenously in six days with satisfactory effect. Following a thoracotomy on June 20 the patient made a rapid convalescence. The fourth patient, S. H., after a positive blood culture on May 10, received 60,000 units of the serum intravenously, with evident favorable effect. Serum was then discontinued. Death occurred on May 26.

It may be superfluous to state that these patients were, as a rule, not under our control, but were seen in consultation. In some instances, particularly when the outlook appeared most grave, the serum treatment was willingly accepted. Sometimes the administration of the serum was later interrupted. We think that further serum therapy would have been helpful in some of these instances.

#### SUMMARY AND CONCLUSIONS

1. Thirteen patients with conditions ordinarily classified in the field of general surgery, infected with hemolytic streptococci, were treated with the concentrated streptococcus serum of the laboratory of the New York State Department of Health. Eight survived and five died.

2. In one patient after the serum therapy had been discontinued streptococcic septicemia developed and death occurred. Two patients were treated with serum after positive blood cultures were obtained, and in both the blood became sterile. One of these recovered.

3. The serum is strongly recommended for infection of the hand in physicians, nurses and laboratory personnel, a type of lesion with dangerous possibilities when infected with hemolytic streptococci.

4. In accidental and in operative wounds, streptococcic infection should be treated with streptococcus serum.

5. Care should be exercised in the desensitization of patients who may be hypersensitive to horse serum.

## SIGNIFICANCE OF ANAEROBIC ORGANISMS IN PERITONITIS DUE TO LIVER AUTOLYSIS

A BACTERIOLOGIC STUDY OF THE PERITONEAL EXUDATES

HAROLD M. TRUSLER, M.D.

JAMES R. REEVES, M.D.

AND

HUGH E. MARTIN, A.M.

INDIANAPOLIS

The medical literature of the past twenty years contains numerous reports designating the Welch bacillus as a factor in the etiology of various pathologic conditions, both clinical and experimental. The most recent are the reports of Andrews, Rewbridge and Hrdina, who contended that the Welch bacillus is the cause of death following the intra-peritoneal introduction of various sterile preparations of liver and of bile salts. These investigators made their observations on dogs and concluded that the Welch bacillus is a normal inhabitant of dog tissue. In view of the fact that these observations resulted from experimental work on liver autolysis, a brief review of the literature is indicated.

Mann<sup>1</sup> in his studies on the effect of hepatectomy in the dog observed that if a small piece of the liver was allowed to remain in the peritoneal cavity the animal died much sooner than if the liver was entirely removed. Mason, Davidson, Matthew and Rastello,<sup>2</sup> thinking that there might be some relation between the death of the dogs and the toxic manifestations encountered after the intravenous administration of an anticoagulant from dog liver, studied the effect of placing small pieces of aseptically removed liver in the peritoneal cavity of dogs. Their conclusions were that this autolysis of the liver in vivo produces a powerful toxin which on absorption causes death in a few hours. Ellis and Dragstedt<sup>3</sup> studied the autolysis of dog liver in vivo and con-

From the Research Division, Indiana University School of Medicine.

1. Mann, F. C.: Personal communication to the authors.

2. Mason, E. C.; Davidson, E. C.; Matthew, C. W., and Rastello, P. B.: A Study of Tissue Autolysis in Vivo, *J. Lab. & Clin. Med.* 10:622 (May) 1925.  
Mason, E. C.; Davidson, E. C., and Rastello, P. B.: Study of Tissue Autolysis in Vivo: Pharmacological Study of Toxic Material, *ibid.* 10:906 (Aug.) 1925.  
Mason, E. C.; Davidson, E. C., and Matthew, C. W.: Tissue Autolysis in Vivo; Observations Using Spleen, *ibid.* 10:997 (Sept.) 1925.

3. Ellis, J. C., and Dragstedt, L. R.: Liver Autolysis in Vivo, *Arch. Surg.* 20:8 (Jan.) 1930.

cluded that death of the dogs is due to bacterial peritonitis. They described the bacterium as being a large, gram-positive, gas-forming anaerobic bacillus which is normally present in the liver of the adult dog and is similar to, but not identical with, the Welch bacillus. Andrews and Hrdina,<sup>4</sup> believing that the dogs die too soon after the introduction of the liver substance for their death to be due to an ordinary infectious process, and observing large quantities of gas in the peritoneal cavity, concluded that the offending organism is the Welch bacillus and that the dogs die as the result of toxemia caused by the Welch bacillus. They further reported that this infection can be induced by the implantation of liver substance previously sterilized by autoclaving, and concluded that there resides in the implanted material some toxic substance which makes the infection by the Welch bacillus a practical certainty. They assumed that this organism is a normal inhabitant of dog tissue and invades the peritoneal cavity as a result of the devitalizing action of the toxic material. Rewbridge,<sup>5</sup> after studying peritonitis produced by bile and sterile bile salt solutions, reported that these substances likewise produce fatal peritonitis caused by the Welch bacillus. Andrews, Rewbridge and Hrdina,<sup>6</sup> in a further study, concluded that infection by the Welch bacillus can be initiated in the pelvis, in the chest or in muscular tissue by the injection of sterile bile salt solutions, bile or sterile liver extract.

We have been investigating this problem for the past three years. In certain fundamental respects our results are at complete variance with these sweeping conclusions. Our experiments cover several phases of the rather complex subject. A detailed account of our results will be found in the protocols and tables which follow.

#### GENERAL OBSERVATIONS

We do not find *Clostridium Welchii* to be a normal inhabitant of dog liver or dog muscle. Our experimental methods and the observations substantiating this statement were reported in detail in a previous publication.<sup>7</sup> In a series of normal dogs we were able to demonstrate in liver and muscle tissue gram-positive, gas-forming anaerobic organisms which on superficial study might be confused with the Welch bacillus. These organisms, however, were not identical with *Cl. Welchii* in

---

4. Andrews, E., and Hrdina, L.: The Cause of Death in Liver Autolysis, *Surg., Gynec. & Obst.* 52:61 (Jan.) 1931.

5. Rewbridge, A. G.: The Etiologic Role of Gas-Forming Bacilli in Experimental Bile Peritonitis, *Surg., Gynec. & Obst.* 52:205 (Feb.) 1931.

6. Andrews, S.; Rewbridge, A. G., and Hrdina, L.: Causations of *Bacillus Welchii* Infections in Dogs by the Injection of Sterile Liver Extracts or Bile Salts, *Surg., Gynec. & Obst.* 53:176 (Aug.) 1931.

7. Trusler, H. M., and Reeves, J. R.: The Significance of Anaerobic Organisms in Peritonitis Due to Liver Autolysis, *Arch. Surg.* 28:479 (March) 1934.

morphology or in cultural characteristics. What is more important, in no case could they be shown to produce an exotoxin *in vitro*. We have shown these organisms to constitute several strains of a vaguely classified group of anaerobic, spore-forming saprophytes characterized by their ability to form great quantities of gas during the rapid digestion of protein and to live at high temperature. They usually are gram-positive and in most instances form terminal spores. The conditions under which these organisms cause death in dogs will be discussed later in this paper.

When pieces of liver removed aseptically from one dog are introduced with the usual aseptic precautions into the peritoneal cavity of another dog, death results in a few hours. This is a common observation of many investigators, and a detailed account of this phase of our work is unnecessary. Our observations were made on a series of about thirty dogs, and in every instance we recovered from the peritoneal exudates large, gram-positive, gas-forming anaerobes. These bacteria were identical with the organisms normally found as the bacterial flora of the liver of the adult dog and of dog muscle. In no instance were we able to isolate *Cl. Welchii* or any organism that produced an exotoxin *in vitro*. In general our observations on this phase of the problem were in complete agreement with the results reported by Ellis and Dragstedt. We found, however, that the peritoneal exudate of these dogs contained not only the liver organism but other anaerobes normally found in dog muscle. This fact, together with the observation that staphylococci, streptococci and colon bacilli were also present, caused us to conclude that probably we were contaminating the pieces of liver while placing them in the peritoneal cavity or that possibly the bacteria normally present as the flora of the abdominal wall gained access to the peritoneal cavity through the peritoneal incision.

#### EXPERIMENTS WITH FRESH AUTOCLAVED LIVER

Ellis and Dragstedt reported that when chunks of fresh liver are sterilized by autoclaving before they are introduced into the peritoneal cavity of the dog, the dog suffers no harmful effects. Andrews and Hrdina reported that when 100 Gm. of fresh liver is finely ground and is then autoclaved and introduced into the peritoneal cavity, the dog dies in a few hours with toxemia caused by the Welch bacillus. They explained the difference in their results on the basis that the finely ground liver presents more surface for autolysis and absorption than the autoclaved chunks of liver and that the toxin thus produced is sufficient to cause the invasion of the peritoneal cavity by the Welch bacillus.

We found, contrary to the reports of Andrews and Hrdina, that 100 Gm. of fresh dog liver finely ground and sterilized by autoclaving usually does not cause death when injected aseptically into the dog's peritoneal cavity. It seemed logical to us, as mentioned earlier, that



the intraperitoneal implantation of preparations of liver, using ordinary surgical technic, might result in contamination by the normal flora of the abdominal wall. We therefore decided that the logical method of introducing the liver substance in an uncontaminated state would be by injection. The liver was therefore ground fine enough to be injected through a 15 gage needle.

*Preparation of the Liver Substance.*—In each case the dog from which liver was to be obtained was placed under general ether anesthesia and was prepared for aseptic surgical procedure. The abdomen was split open with hot wire cautery, and the abdominal wall was retracted. The portal vein and the inferior vena cava were ligated, and the liver, removed in a more or less bloodless state, was placed in a large, sterile Petri dish. The liver was immediately prepared as follows: The gallbladder, all the large veins, the connective tissue and the fat were dissected away and the remaining liver substance was passed through a sterile food-grinder. The ground liver was placed in 500 cc. Erlenmeyer flasks, each flask containing 110 Gm. of the ground liver. A small handful of glass beads and 100 cc. of physiologic solution of sodium chloride were added to each flask, and the lot was autoclaved at 15 pounds' (6.8 Kg.) pressure for fifteen minutes. The flasks were then removed from the autoclave and were placed in a mechanical shaker, after the cotton plugs were replaced with sterile rubber stoppers. After a vigorous shaking for forty minutes, the liver was filtered through gauze to remove the glass. The finely divided liver substance resulting was light brown and formed a suspension in the 100 cc. of physiologic solution of sodium chloride. The liver substance was put in 250 cc. Erlenmeyer flasks and was again autoclaved at 15 pounds' pressure for fifteen minutes. The preparation was then set in the icebox to await injection, the cotton plugs being first replaced with sterile rubber stoppers.

*Experiment 1a.*—Two dogs were prepared as for aseptic surgical procedure. A sterile 15 gage needle was pushed through the midline into the peritoneal cavity, and the liver substance was introduced by means of a 30 cc. syringe. We hoped in this way to introduce the needle without penetrating the muscle tissue.

In brief, the results of this experiment were as follows: Both dogs died approximately fifteen hours after the introduction of the liver substance. The dogs were examined with aseptic precaution, and specimens for smears and for cultures were taken of the peritoneal exudate and peritoneal surface. The autopsy observations on both dogs were typical. Needle puncture wounds were found penetrating the rectus muscle of each dog. In each case the abdomen contained about 500 cc. of thin bloody fluid. Both the liver and the spleen showed cloudy swelling but were not crepitant. There was moderate enteritis, most marked in the duodenum. The injected particles of liver were adherent to the omentum. The peritoneal surfaces were markedly injected and fiery red. The cultures and smears all yielded large, gram-positive, gas-forming anaerobes, staphylococci, streptococci and colon bacilli. Subsequent bacteriologic study of the gram-positive anaerobe revealed that it was identical with the anaerobic bacillus normally present in dog muscle. Tests on this organism for toxicity showed that it did not produce an exotoxin in vitro. We were still of the opinion that contamination of the injected liver substance occurred as the needle passed through the abdominal wall. With this in mind the experiment was modified as shown in experiment 1b.

*Experiment 1b.*—Two dogs were prepared for injection as described in experiment 1a. In this instance a slit was burned well through the skin, fascia and muscle in the midline of the dog's abdomen with a wire cautery. Care was taken

not to burn through the peritoneum. The 15 gage needle was then introduced through the cautery incision into the peritoneal cavity. The results of this experiment were different from those observed in experiment 1a. One of the dogs lived indefinitely, and was used some months later in another experiment. The other dog died eleven days later of an extensive pneumonic process involving both lungs. Autopsy of this dog revealed that the abdominal cavity contained no gas or fluid. The liver and spleen were firm and were not crepitant. The lobes of the liver were adherent, with light, filmy adhesions. The omentum was the site of much black pigmentation and was bound to the site of the injection. The peritoneal surfaces were smooth and glistening. There was no sign of exudate on the peritoneal surfaces. A few particles of the injected liver substance were matted to the omentum, from which the normal fat was entirely absent, as if absorption had occurred. The pleural cavity contained from 25 to 30 cc. of dark bloody fluid. Both lungs were extensively involved with a pneumonic process. An account of experiments 1a and 1b will be found in table 1.

TABLE 1 (Experiment 1).—*Bacteriologic Study of Peritoneal Exudate of Dogs Into Which Fresh Finely Ground Dog Liver Sterilized by Autoclaving Was Injected Intra-peritoneally*

Dog	Smear	Culture	Survival	Organism	Exotoxin	Cause of Death
Experiment 1a (Without the Cautery)						
76	Positive	Positive	15 hours	Muscle organism; staphylococcus; streptococcus; colon bacillus	None	General peritonitis
77	Positive	Positive	15 hours	Muscle organism; staphylococcus; streptococcus; colon bacillus	None	General peritonitis
Experiment 1b (With the Cautery)						
597	None taken	None taken	Survived	None	None	Dog survived
598	None taken	None taken	11 days	None	None	Pneumonia; no peritonitis

We showed that when the liver was introduced aseptically by means of a small cautery incision through the skin, fascia and muscle and a needle puncture through the intact peritoneum, two dogs survived the injection, but that when the needle was inserted through the abdominal wall without cautery two dogs died of bacterial peritonitis. This observation led us to believe that finely ground fresh liver substance sterilized by autoclaving does not cause the death of the dog if the material is not contaminated in the process of its introduction.

The object of our next experiment was further to substantiate the thought that finely ground, sterile liver introduced in an uncontaminated state remained uncontaminated until absorbed. To prove this point it seemed necessary to remove samples of peritoneal exudate from the dog's peritoneal cavity for culture and smear from time to time following the introduction of the liver material. An attempt to aspirate peritoneal exudate through a 15 gage needle was more or less unsuccessful, but we found that by using a needle perforated in several places

near the beveled end peritoneal exudate can be aspirated successfully. This method was used in experiment 2.

*Experiment 2.*—Liver substance was injected into four dogs in the same manner as was described for experiment 1*b*. As an added precaution against contamination the needle was heated red-hot before it was introduced through the cautery slit. The substance was successfully injected into three of the dogs in this manner. In the other dog a portion of the liver substance was inadvertently injected into the abdominal wall before it was seen that the needle had not completely entered the peritoneal cavity. The dogs were examined eighteen hours later. The dog with a portion of the liver preparation injected into the abdominal wall was dead and in rigor. The other three dogs were lying on their sides, breathing deeply. They were not comatose, however, and were able to stand when placed on their feet.

TABLE 2 (*Experiment 2*).—*Bacteriologic Study of Peritoneal Exudate of Dogs Into Which Fresh, Finely Ground Liver Sterilized by Autoclaving Was Injected Intraperitoneally*

Dog	Samples Removed After 18 Hours	Survival	Autopsy
837	Smear and culture, negative	Killed after 2 weeks	No peritonitis; no fluid or gas in the peritoneal cavity; spleen and liver normal as to color and consistency; peritoneal surfaces smooth and glistening
838	Smear: positive for gram-positive bacilli and other contaminants  Culture: positive for gram-positive bacilli and other contaminants	Found dead and in rigor in 18 hours	Some of the liver substance was injected by mistake into the abdominal wall; as a result examination showed: right rectus muscle necrotic and blown up with gas; general peritonitis with gas and turbid brown fluid in the peritoneal cavity, caused by direct extension of the infection through the peritoneal puncture
839	Smear and culture, negative	Alive after 6 months	Not killed
840	Smear and culture, negative	Killed after 3 months	No peritonitis; peritoneal surfaces smooth and glistening; liver and spleen normal as to color and consistency; a few filmy adhesions between the lobes of the liver

After the intracutaneous injection of a 1 per cent solution of procaine hydrochloride as an anesthetic, a specimen of peritoneal exudate was aspirated from each dog for culture and smear. To obtain the fluid a perforated 15 gage needle was introduced with the same cautery technic employed in the original injection. The peritoneal exudate of the living dogs was clear and blood-tinged, while that of the dead dog was turbid and dark brown. All cultures and smears of the peritoneal exudate of the living dogs were negative for bacteria, while both the smear and the culture of the peritoneal exudate of the dead dog yielded a gram-positive, gas-forming anaerobe which proved on further study to be the organism normally present in the muscle.

Autopsy of the dead dog revealed the right rectus muscle to be necrotic and blown up with gas. There was generalized peritonitis. The liver and spleen were not crepitant, although there were gas and a quantity of fluid in the peritoneal cavity. The three living dogs continued to improve and were able to partake of food and water on the third day. At the end of forty-eight hours an attempt was made to aspirate some of the peritoneal exudate from one of the dogs for smear

and culture, but no fluid could be obtained from the peritoneal cavity. One of the dogs was killed two weeks following the implantation of the liver substance. The general condition of the dog was good. Examination revealed complete healing of the cautery wounds in the abdomen. The peritoneal surfaces were smooth and glistening. There were no signs of peritonitis. The liver and spleen were normal as to color and consistency. The only evidence of the previously injected liver substance was an occasional minute particle caught in the omentum. Light, filmy adhesions were found between the lobes of the liver and between the liver and the diaphragm. The other two dogs were kept under constant observation, and except for a tendency to become extraordinarily fat no other observations of clinical interest were noted. One of the dogs was killed three months following the implantation of the liver. Autopsy revealed essentially a normal peritoneum. The light, filmy adhesions found in the first dog were between the lobes of the liver and between the liver and the diaphragm. There was a great deal of fatty infiltration about the viscera. The omentum was completely regenerated and contained a few areas of brownish pigmentation. The other dog was alive and apparently normal six months after the introduction of the liver substance. Table 2 gives an account of the experiment.

In experiment 2 we found that in three dogs 100 Gm. of fresh autoclaved liver, when injected aseptically into the peritoneal cavity, did not cause death. The material made the animal ill for a few days. However, one dog (838) in the series died, and in this case there was evidence of bacterial peritonitis associated with the infection in the wound caused by injecting the material into the abdominal muscles. The infection was due to organisms normally found in the abdominal wall of the dog. At autopsy we found the needle puncture wound digested and the infection extended into the peritoneal cavity. Obviously the material forms an ideal culture medium and when contaminated in any way causes death in a manner similar to that observed when fresh liver containing its normal flora is introduced into the peritoneal cavity. We have shown, however, that when 100 Gm. of fresh, finely ground, autoclaved liver is injected intraperitoneally in an uncontaminated state it remains sterile until absorbed and will not cause the death of a normal, healthy dog.

#### EXPERIMENTS WITH INCUBATED LIVER

Andrews and Hrdina reported toxemia caused by the Welch bacillus as a terminal event after the intraperitoneal introduction of dog liver which had been incubated and then sterilized by autoclaving. In an effort to substantiate these observations we conducted a series of experiments. The technic employed in injecting the liver substance and in aspirating the peritoneal exudates for bacterial smear and culture was the same as that employed in experiment 2.

*Preparation of Incubated Liver.*—We wish to point out that the nature of the incubated liver substance is different according to whether it is incubated with only the normal flora present or before incubation is contaminated with other

bacteria. The livers were removed from dogs in the same bloodless, aseptic manner described earlier in this paper. The linen, grinder, physiologic solution of sodium chloride and instruments and everything coming in contact with the liver were autoclaved. The technician was gowned, gloved and masked as for an aseptic surgical procedure. As an added precaution the livers were thoroughly scalded with autoclaved distilled water just before they were ground and placed in the sterile Erlenmeyer flasks. Three preparations of the incubated liver were made. One preparation was incubated for twenty-four hours, another for forty-eight hours and the third, for seventy-two hours. Sterilization in the autoclave, shaking, filtering and resterilization in the autoclave were done in the same manner as described for the preparations of fresh liver.

As was mentioned previously, the anaerobic bacterial flora of the normal adult dog liver enters actively into the digestion of the liver substance when the liver is incubated. Digestion is rapid, great quantities of gas being produced in twenty-four hours. The process continues for forty-eight hours and more but in most cases is complete in seventy-two hours. After autoclaving the material is dark brown with a pungent odor that is not putrefactive unless the liver has been contaminated with extraneous bacteria before incubation.

*Experiment 3.*—Four dogs were used in this experiment. One hundred grams of ground liver incubated for twenty-four hours and sterilized by autoclaving was injected intraperitoneally into each dog. Eighteen hours later two dogs were dead and the other two were prostrate and dyspneic. One of the dead animals showed rigor and too much postmortem change to justify any bacteriologic study. In the other it was apparent that death was recent, and material for smears and culture was taken from the peritoneal exudate of this animal. No gram-positive bacteria were found on the smear, but the culture was positive for gas-forming bacilli after incubation for eighteen hours at 40 C. Subsequent study and tests for toxicity on the gram-positive organism in this culture proved that it was the organism normally present in the muscle and that it did not produce an exotoxin in vitro.

Samples of the peritoneal exudate were removed from the two living dogs fourteen hours after the introduction of the liver material. All the smears and cultures of these specimens of peritoneal exudate were negative for bacteria. One of these two dogs was found dead nine hours later, twenty-three hours after the liver was injected. A sample of peritoneal exudate was removed from the other dog twenty-three and a half hours after the injection of the liver material. The dog was prostrate and more or less comatose at this time. Both the smear and the culture were negative for bacteria. When the dog was examined fourteen hours later his condition was much improved, and no sample of peritoneal exudate was taken. Six weeks later the dog was still living but was gaunt and emaciated. The dog died four or five days later and was cremated by an inexperienced caretaker before an autopsy could be performed.

The smears of the peritoneal exudate of dogs into which was injected the liver substance which was incubated are more or less difficult of interpretation; sterilization in the autoclave, although it kills the bacteria does not cause the disintegration of the bacterial bodies. Consequently all the smears of the peritoneal exudate of dogs into which this material was injected were positive for bacterial forms. These forms, however, stained gram-negative, had fuzzy outlines and were granular. If stains are made of the incubated liver preparation immediately after it is autoclaved, many of the bacterial forms stain gram-positive. After a week or so in the icebox these bacterial forms always take a gram-negative stain. We

interpreted as positive those smears which showed the presence of large, clearcut bacterial bodies which stained a definite gram-positive, or any stained smear was considered positive which showed the presence of staphylococci, streptococci or colon bacilli.

Typical postmortem observations on the dogs which died as the result of the intraperitoneal injection of the incubated liver preparations were as follows: The abdomen contained about 500 cc. of thin bloody fluid. The injected liver particles were caught in the omentum. The omentum and all the peritoneal surfaces were markedly congested and fiery red. There was no free gas in the peritoneal cavity. The liver and spleen showed cloudy swelling but were not crepitant. There was severe enteritis in the entire alimentary tract, most severe in the duodenum. The intestines, stomach and urinary bladder were usually contracted. The abdominal wall was edematous and the superficial veins were engorged with blood. An account of the experiment is given in table 3.

TABLE 3 (Experiment 3).—*Bacteriologic Study of Peritoneal Exudate of Dogs Into Which Finely Ground Liver Incubated for Twenty-Four Hours and Sterilized by Autoclaving Was Injected Intraperitoneally*

Dog	First Sample	Subsequent Samples	Survival	Autopsy
841	14 hours: smear and culture negative	None taken	Dead and in rigor in 23 hours	No examination
842	Smear and culture not made	.....	Dead and in rigor in 12 hours	No examination
843	14 hours: smear and culture negative	23½ hours: smear and culture negative	Six weeks	Dog was cremated before autopsy could be done
844	12 hours: smear and culture, positive for gram-positive bacilli and other contaminants	.....	Dead in 12 hours; rigor had not set in	Abdomen contained about 500 cc. of blood-tinged fluid; no free gas in the abdomen; liver and spleen not crepitant; marked enteritis

Experiment 3 proved that 100 Gm. of ground liver incubated for twenty-four hours and sterilized in the autoclave is much more toxic to the dog than ground fresh autoclaved liver. The incubated liver usually causes the death of the dog in a few hours, although in this experiment one of the animals survived the injection for about six weeks.

We were of the opinion that the dogs into which this material was injected did not have bacterial peritonitis before they died, although the experiment did not definitely prove this. All the smears and cultures of the peritoneal exudate removed from these dogs before death were sterile. It seemed that the bacterial invasion of the peritoneal cavity occurred only after the dog died, but in order to be sure of this it was obvious that a more careful watch of the dogs was necessary, for the purpose of culturing the peritoneal exudate at the time of death. To do this and at the same time to see if the forty-eight hour incubated liver substance was more toxic than the twenty-four hour incubated liver, experiment 4 was carried out.

*Experiment 4.*—Three dogs were used. The experimental methods and observations were identical with those employed in experiment 3, except that in this instance ground liver which had been incubated for forty-eight hours and then sterilized by autoclaving was injected intraperitoneally. All three dogs died as the result of the injection. One of the dogs died twelve hours after the injection; one from eighteen to twenty-one hours after the injection, and the third, twenty-two hours after the injection. Cultures and smears of the peritoneal exudate removed from the peritoneal cavities of the three dogs twelve hours after the injection of the liver material were all negative for bacteria. One of the dogs died as the exudate was being removed from the peritoneal cavity. One of the remaining dogs died eight hours later before a second sample of exudate could be taken. A sample of peritoneal exudate was removed from the other dog just a few minutes before the dog died. The culture and smear of this sample were both negative. An account of the experiment is given in table 4.

TABLE 4 (*Experiment 4*).—*Bacteriologic Study of Peritoneal Exudate of Dogs Into Which Finely Ground Liver Incubated for Forty-Eight Hours and Sterilized by Autoclaving Was Injected Intraperitoneally*

Dog	First Sample	Subsequent Samples	Survival	Autopsy
845	12 hours: smear and culture, negative*	.....	12 hours	No bacterial peritonitis; no gas in the peritoneal cavity; marked enteritis; about 500 cc. of blood-tinged fluid in the peritoneal cavity
846	12 hours: smear and culture, negative	None taken	Dead and in rigor in 20 hours	No examination
847	12 hours: smear and culture, negative	22 hours: smear and culture negative*	22 hours	Observations same as those for dog 845

\* Sample of peritoneal exudate was removed as the dog was dying.

In experiment 4, smears and cultures of specimens of peritoneal exudate from the three dogs taken twelve hours after the injection of the liver substance were all negative for bacteria. In the case of two dogs smears and cultures of specimens taken at the time of death were likewise negative. There was no reason to believe that bacterial peritonitis developed before death.

It was evident that this material was much more toxic to the dog than the liver incubated for twenty-four hours. The dogs were obviously in a greater state of shock. In an effort to determine whether or not a still more toxic material would alter the bacteriologic results, liver incubated for seventy-two hours was injected into four dogs. This was experiment 5.

*Experiment 5.*—Ground liver incubated for seventy-two hours and sterilized by autoclaving was injected intraperitoneally into four dogs. The technic was the same as that employed in the preceding experiments with incubated liver. One dog was found dead five hours following the injection. Both the culture and the smear

of the peritoneal exudate contained gram-positive bacteria, staphylococci, streptococci and colon bacilli. The gram-positive organism was not *Cl. Welchii*.

One dog was prostrate and comatose in five hours. Both the culture and the smear of the peritoneal exudate removed at this time were negative for bacteria. One-half hour later, as the dog was dying, a second specimen of the peritoneal exudate was removed. The culture and smear of this specimen were likewise negative. A third sample was removed one-half hour post mortem. This sample was negative for bacteria on culture and on smear.

The other two dogs were prostrate, but reacted and were therefore kept under observation. Twenty-four hours after the injection of the liver material samples of peritoneal exudate were removed from both dogs. Both the smear and the culture of the peritoneal exudate removed from one of the dogs were negative. A sample of peritoneal exudate was removed from the same dog six hours later.

TABLE 5 (*Experiment 5*).—*Bacteriologic Study of Peritoneal Exudate of Dogs Into Which Finely Ground Liver Incubated for Seventy-Two Hours and Sterilized by Autoclaving Was Injected Intraperitoneally*

Dog	First Sample	Second Sample	Third Sample	Survival	Autopsy
849	5 hours: smear and culture, positive; dog dead	1½ hours post mortem: smear and culture, positive	None taken	Found dead in 5 hours; no rigor	No gas in the peritoneal cavity; liver and spleen not crepitant; about 300 cc. of bloody fluid in the peritoneal cavity; much injection of the peritoneal surfaces; marked enteritis
850	24 hours: smear, negative; culture, positive	27 hours: smear, negative; culture, positive*	1½ hours post mortem: smear and culture, negative	27 hours	Same as for dog 849
851	24 hours: smear and culture, negative	30 hours: smear and culture, negative	1½ hours post mortem: smear and culture, positive	35½ hours	Same as for dog 849
852	5 hours: smear and culture, negative	5½ hours: smear and culture, negative*	½ hour post mortem: smear and culture, negative	5½ hours	Same as for dog 849

\* This sample of peritoneal exudate was removed as the dog was dying.

It was likewise negative for bacteria. Five hours after the removal of the second sample the dog died. A third sample of peritoneal exudate was removed one and one-half hours post mortem. Both the smear and the culture of this sample of peritoneal exudate were positive for bacteria of many kinds.

The observations on the remaining dog of the series were unusual. Three samples of peritoneal exudate were removed. The first sample was removed three hours before death, the second as the dog died, and the third one and one-half hours post mortem. The smears were all negative for bacteria. Both cultures taken before death were positive for gram-positive anaerobes, staphylococci and streptococci, while the third culture, taken one and one-half hours post mortem, was negative for bacterial growth. This unusual result could be explained only on the grounds of contamination. The results of this experiment are found in table 5.

The experiments with incubated liver showed that dogs always die following the intraperitoneal injection of this preparation, usually in a



few hours. The peritoneum of several of the dogs into which the incubated liver was injected was shown by culture and by smear of the peritoneal exudate to be sterile at death. On the other hand, the peritoneal exudate of several of the dogs was shown by culture to be contaminated with gram-positive, gas-forming anaerobic bacilli, staphylococci, streptococci and colon bacilli. The essential fact is that preparations of fresh liver which are allowed to incubate from twenty-four to seventy-two hours before being sterilized contain in themselves some toxic factor which is sufficient to cause the death of the dog in every instance. When a sample of peritoneal exudate yielded a gram-positive, gas-forming anaerobe, subsequent isolation and study of the organism proved it in most instances to be the organism commonly found in the muscle of normal adult dogs. In no instance were we able to isolate *Cl. Welchii* or any organism that produced an exotoxin in vitro. The fact that smears were repeatedly negative for living bacterial forms, that positive cultures were usually associated with common contaminants and that our observations were variable led us to believe that contamination was still a great factor in our results. It is true that when fresh autoclaved liver was injected subsequent cultures of the peritoneal exudate were almost uniformly negative, indicating that under these conditions the technic of cautery and needle puncture was adequate to prevent contamination. When, however, a dog was prostrated and dying from the shock of the highly toxic incubated and autoclaved liver, the peritoneal cavity was more easily infected by the insertion of a large needle through the abdominal wall. This belief was strengthened by the observation that the toxic incubated suspensions of liver caused marked venous engorgement and edema of the abdominal wall. Cautery burns and perforations by a hot needle of this highly vascular and edematous tissue could be the source of bacterial contamination of the peritoneal cavity. Some procedure for introducing the material into and aspirating peritoneal fluid from the abdominal cavity with more strict bacteriologic technic seemed necessary. Therefore, a method was devised, as used in experiment 6.

*Experiment 6.*—By careful aseptic surgical procedure a small area of the peritoneum of the dog was exposed through an incision in the lower right quadrant of the abdomen about 1 inch (2.5 cm.) from the midline. The peritoneum at this point is continuous with the aponeurosis of the internal oblique muscle and forms a tough, resistant structure. The skin was opened with a cautery, and the muscles were separated with as little trauma and bleeding as possible. The instruments used for the operation were thoroughly phenolized as well as boiled before they were used. The exposed peritoneum was grasped with two mosquito forceps and lifted out of the peritoneal cavity. A purse-string suture of sterile, strong silk was sewed in the peritoneum about the clamps. A small incision about  $\frac{3}{8}$  inch (0.9 cm.) long was made through the peritoneum inside the purse-string suture. The edges of the cut peritoneum were grasped with mosquito forceps and turned outward. The end of a sterile glass tube especially designed for the pur-

pose was inserted through the opening, and the peritoneum was tied tightly about the first constriction of the tube. The tube was pulled outward, and the peritoneum was again tied securely about the second constriction. This procedure firmly anchored the tube to the peritoneum and made a bacteria-tight closure about the tube. The abdominal incision was then carefully closed about the tube, care being taken not to tie off or devitalize any muscle tissue. Figure 1 illustrates the nature of the tube and the manner of its insertion. The tube can easily be made from glass test tubes, and by first searing the vaccine bottle stopper with a wire cautery any number of samples of peritoneal exudate can be removed in an uncon-

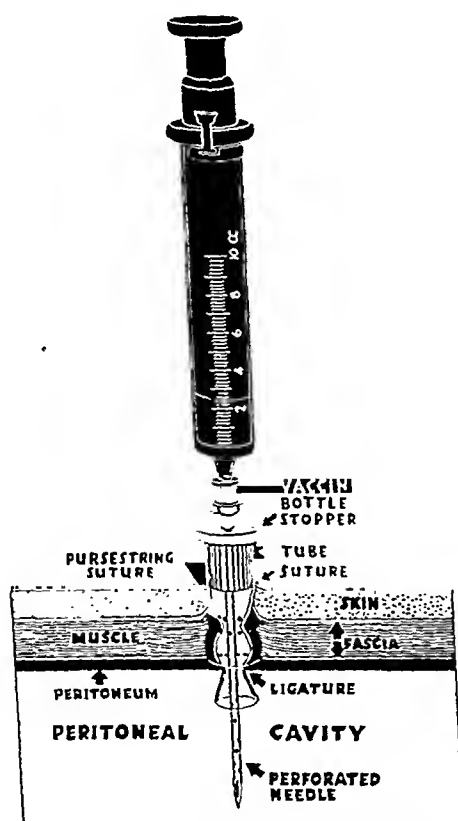


Fig. 1.—A diagram showing the insertion of the tube used to obtain uncontaminated samples of peritoneal exudate from the dog's peritoneal cavity.

taminated state. Likewise, any material that can be injected through a hypodermic needle can be introduced intraperitoneally in an uncontaminated state. This arrangement has proved ideal for any study of the peritoneal exudate of dogs taking place over a period of from thirty to forty-eight hours following the placing of the tube. After a time the peritoneum devitalized by the grasp of the retaining sutures will slough, and the point of the insertion of the tube will no longer be bacteriologically tight.

By using this technic the following experiment was carried out: The tube was anchored to the peritoneum of three dogs in the manner described. One hour after

the insertion of the tube 100 Gm. of ground sterile liver incubated for seventy-two hours was injected into one dog. Liver incubated for forty-eight hours was injected into another dog, and liver incubated for twenty-four hours was injected into the third. The preparation of the liver was the same as that described earlier in this paper. Samples of peritoneal exudate were removed at one and a half and two hour intervals until the death of the dogs. The dogs were kept in a lethargic and painless state by the intramuscular injection of small amounts of morphine and sodium amytal. In brief, the results of the experiment were as follows:

The dog into which the liver, incubated for seventy-two hours, was injected died in nine hours. During this time five consecutive samples of the peritoneal exudate

TABLE 6 (*Experiment 6*).—*Bacteriologic Study of Peritoneal Exudates, Samples of Which Were Removed Through the Tube Described in Experiment 6*

Dog	Liver Incubated for	Samples	Time Taken	Smears	Culture
951	72 hours	1	2 hours	Negative	Negative
		2	3½ hours	Negative	Negative
		3	5 hours	Negative	Negative
		4	6½ hours	Negative	Negative
		5	8 hours	Negative	Negative
		6*	9 hours	Negative	Negative
		7†	10 hours	Negative	Negative
		8‡	11 hours	Negative	Positive
954	48 hours	1	15 minutes	Negative	Negative
		2	2½ hours	Negative	Negative
		3	4½ hours	Negative	Negative
		4	6½ hours	Negative	Negative
		5	8½ hours	Negative	Negative
		6	10½ hours	Negative	Negative
		7	12½ hours	Negative	Negative
		8	14½ hours	Negative	Negative
		9	16½ hours	Negative	Negative
		10	19 hours	Negative	Negative
		11	22 hours	Negative	Negative
		12*	24 hours	Negative	Negative
		13†	25 hours	Negative	Negative
955	24 hours	1	15 minutes	Negative	Negative
		2	2½ hours	Negative	Negative
		3*	5½ hours	Negative	Negative
		4†	6½ hours	Negative	Positive
		5‡	7½ hours	Negative	Positive
		6§	9½ hours	Negative	Positive

\* This sample was removed as the dog died.

† This sample was removed one hour post mortem.

‡ This sample was removed two hours post mortem.

§ This sample was removed four hours post mortem.

were removed for bacteriologic smear and culture. One sample was taken as the dog was dying. Two samples taken subsequently were removed one and two hours post mortem. All smears, including the one taken two hours post mortem, were negative for bacterial growths. Cultures of the first seven samples of peritoneal exudate removed, including the one removed one hour post mortem, were also negative. Culture of the sample of peritoneal exudate removed two hours post mortem was positive for bacterial growth after incubation for eighteen hours at 40 C. Subsequent study of the organism showed that it was present in the exudate in pure culture and that it was identical with the organism commonly found in dog muscle.

The second dog, into which was injected liver material incubated for forty-eight hours, lived for twenty-four hours. During this time thirteen consecutive samples of the peritoneal exudate were removed. All the smears of these samples were

negative for bacteria. Cultures taken of the peritoneal samples were likewise negative for bacterial growth. The last sample was removed one hour post mortem.

The third dog, into which was injected liver material incubated for twenty-four hours, lived for five and one-half hours. Three samples of peritoneal exudate were removed from this dog while it was still living, the third sample being removed as the dog was dying. Three samples taken subsequently were removed one, two and four hours post mortem. Smears of all six of the samples were negative for bacteria, while cultures of the three samples removed post mortem showed bacterial growth. Bacteriologic study of the positive cultures showed a gram-positive anaerobe that existed in the peritoneal exudate in pure culture. This organism was likewise identical with the organism normally present in the muscle tissue of adult dogs. An account of the experiment is given in table 6.

The technic described in experiment 6 enabled us to collect numerous sterile cultures from the peritoneal exudate of dogs dying as a result of the toxic injection. With these meager data we are not prepared to say that all normal dogs have a sterile peritoneum. We have proved, however, that the incubated liver is sufficient in itself to cause the death of the dog. We believe that any bacterial growth found in the peritoneal cavity in the experiments reported earlier is probably due to contamination. We seriously doubt the possibility of the incubated liver material ever causing the antemortem invasion of the peritoneal cavity by bacteria. We are certain that in these experiments it has not caused the invasion of the peritoneal cavity by *Cl. Welchii* during life. It seems that dogs receiving ground, incubated, sterile liver intraperitoneally die with a sterile peritoneum. In two of the dogs in experiment 6 the peritoneum remained sterile as long as one hour post mortem.

#### EXPERIMENTS WITH STERILE SOLUTIONS OF BILE SALTS

Rewbridge and Andrews, Rewbridge and Hrdina have reported that a 10 per cent sterile solution of bile salts (5 cc. per kilogram) is uniformly fatal to the dog when it is introduced intraperitoneally. In their opinion death is due to peritonitis caused by the Welch bacillus induced by the intraperitoneal implantation of the bile salt solutions. It has long been known that bile salts are toxic per se, but Rewbridge reported that the bile salts are not absorbed into the blood stream to toxic levels sufficient to cause the death of the dogs. He concluded that death is caused by the devitalizing action of the bile salts on the peritoneum, bringing about a subsequent invasion of the peritoneal cavity by the Welch bacillus, which he considered to be a normal inhabitant of dog tissues. Our observations on this phase of the subject are the result of experiment 7.

*Experiment 7.*—As we were uncertain whether autoclaving would affect the toxicity or otherwise change the character of the bile salts, we prepared two

different solutions. One solution was sterilized by passing it through a Berkefeld candle, and the other, by autoclaving. Both preparations were proved sterile by culture. A 10 per cent solution of bile salts was prepared by dissolving equal quantities of sodium taurocholate and sodium glycocholate in distilled water. Andrews, Rewbridge and Hrdina having reported that 5 cc. per kilogram of such a solution was uniformly fatal to the dog, we used that amount in our experiments.

Four dogs were prepared in the usual way for aseptic surgical procedure. In two of the dogs a glass tube was anchored to the peritoneum in the manner described in experiment 6. Each of these dogs received an intraperitoneal injection of the bile salt solution through the tube. In one case, bile salts sterilized by passage through the Berkefeld filter were used, and in the other, autoclaved bile salts.

With the thought that in case the animal survived the presence of the tube might vitiate later observations, we employed a different technic in injecting the solution into the other two dogs. In these animals the peritoneum was exposed, but instead of the tubes being anchored a 15 gage needle was inserted and tied with a purse-string suture to the peritoneum. After the bile salt solution was injected the needle was withdrawn, and the perforation of the peritoneum was closed by the suture. The incisions were then repaired. The four dogs were kept under constant observation.

The results of this experiment were as follows: All four dogs died, those receiving the bile salt solutions sterilized by passage through the Berkefeld filter dying first. Five samples of peritoneal exudate were removed from the dog which had received through the tube the bile salt solution sterilized by filtration. The first sample was taken one hour following the injection and the second, four hours later as the dog was dying; the other three samples were removed one, two and three hours post mortem. No bacteria of any kind were found on stained smears of these samples. Cultures of the first three samples, including the one taken one hour post mortem, were negative for bacterial growth. Cultures of the last two postmortem specimens were positive for bacterial growth, even though no bacteria were seen in the smears.

Three samples of peritoneal exudate were removed from the dog which had received the autoclaved bile salt solution through the tube. This dog survived the injection twenty hours. The first sample was removed five hours after the injection of the bile salts, the second four hours later and the last one and one-half hours post mortem. Smears of the first two samples revealed an occasional gram-positive rod, but no other bacteria. A smear of the sample taken post mortem revealed bacteria of many kinds. Cultures of all three samples showed a growth of different kinds of organisms. This result was explained when the dog was examined at autopsy. At this time we found the stomach full of bones, with a perforation in the lower border of the fundus about 1 cm. in diameter. This had the appearance of an old ulcer, and microscopic section confirmed this diagnosis. Obviously this perforation of the stomach contaminated the peritoneal cavity. For that reason no effort was made to isolate or to determine the morphology of the bacteria present in the cultures. We mention these findings only to complete the series.

The two dogs which received the injection of the bile salt solution through the needle were closely watched in order to obtain cultures at the time of death. In each instance, as the dog was dying a needle was inserted through a small cauterized wound in the abdominal wall and samples of peritoneal exudate were removed.

Cultures and smears of both these samples were negative for bacteria. In general, these dogs presented the same picture of prostration and shock as was observed when the incubated liver preparations were injected.

Autopsy observations on the dogs were similar, with the exception of those on the dog with the perforated stomach. In this animal there was a large amount of brownish-red turbid fluid and free gas in the peritoneal cavity. The other three dogs presented the following findings: The peritoneum and omentum were moderately injected. The peritoneal cavity contained about 500 cc. of bright red fluid. The liver and spleen were swollen but firm and not crepitant. Enteritis

TABLE 7 (Experiment 7).—*Bacteriologic Study of Peritoneal Exudate of Dogs Into Which Sterile Solution of Bile Salts Was Injected Intraperitoneally*

Dog	Samples	Smears	Culture	Survival	Autopsy
Solution Sterilized by Autoclaving					
939	1 hour	Positive	Positive	20 hours	Congestion of the peritoneal surfaces and omentum; 500 cc. of brownish-red turbid fluid in the peritoneal cavity; marked enteritis in the ileum, less marked in the rest of the gastro-intestinal tract; distended gallbladder; perforated ulcer in the lower margin of the fundus of the stomach
	5 hours	Positive	Positive		
	1½ hours post mortem	Positive	Positive		
961	Removed as dog died	Negative	Negative	8 hours	Moderate congestion of the peritoneal surfaces and omentum; 500 cc. of bright red fluid in the peritoneal cavity; marked enteritis in the ileum, less marked in the rest of the gastro-intestinal tract; marked contraction of the ileum; distended gallbladder; laked blood in the peritoneal cavity
Solution Sterilized by Berkefeld Filter					
960	1 hour	Negative	Negative	5 hours	Same as for dog 961
	5 hours	Negative	Negative		
	1 hour post mortem	Negative	Negative		
	2 hours post mortem	Negative	Positive		
	3 hours post mortem	Negative	Positive		
962	Removed as dog died	Negative	Negative	.....	Same as for dog 961

was marked in the ileum, but was less marked in the rest of the gastro-intestinal tract. The ileum was tightly contracted throughout its entire extent. The jejunum and duodenum were moderately distended with gas. The large intestine was moderately contracted. The gallbladder in every instance was swollen and tense with bile. There was no gas present in the peritoneal cavity. It interested us to note that within one-half hour after the injection of the bile salts the peritoneal exudate was bright red due to laking of the extravasated blood. An account of the results of this experiment is given in table 7.

Experiment 7 proved that this concentration of equal amounts of the two bile salts, when injected into the peritoneal cavity of the normal adult dog, will cause death in a few hours. In our opinion, this observation has no clinical significance. A 10 per cent solution of the two

bile salts is in no way comparable to bile which one may encounter in the peritoneal cavity under ordinary conditions.

The fact that the dogs die with a sterile peritoneum is conclusive evidence that death is not due to peritonitis caused by the Welch bacillus and that the peritoneum is not invaded by bacteria of any kind as a result of the presence of bile salts *per se*. In view of Rewbridge's conclusion that in these concentrations bile salts are not absorbed into the blood stream to lethal levels, an interesting question arises as to what is the mechanism of death. For the present, we state merely that death occurs without bacterial peritonitis.

#### COMMENT

In the experiments described we made many observations which do not confirm the reports of previous investigators. Andrews, Rewbridge and Hrdina stated that in all phases of this complex experimental problem death is due to toxemia caused by the Welch bacillus. They employed the terms "autolytic peritonitis" and "in vivo autolysis" to designate conditions in which the sterile preparations of liver and of bile salts cause death when introduced intraperitoneally. At autopsy on their animals they found violent bacterial peritonitis, with the formation of gas in the peritoneal cavity as well as in the liver and other tissues. They concluded that the toxic substances injected, even though sterile, caused an autolytic process that resulted in an invasion of the peritoneal cavity by the Welch bacillus, which they stated is normally present in dog tissue.

We have shown that the liver of the normal dog contains an anaerobic bacterial flora and that when pieces of the liver are introduced into the peritoneal cavity of the dog, death results in a few hours and is associated with bacterial peritonitis. When, however, fresh liver is finely ground and sterilized by autoclaving it may be placed in the peritoneal cavity without causing death, provided it is not contaminated. If, on the other hand, the fresh liver is allowed to incubate before being sterilized in the autoclave, bacterial decomposition produces a highly toxic substance, the intraperitoneal injection of which causes death in a few hours, with the animal manifesting a state of profound shock. We have shown that death occurs without bacterial growth in the peritoneal cavity. The same observation was made in the experiments on the intraperitoneal injection of bile salts. These differences have been demonstrated by a careful examination of the peritoneal exudate and postmortem observations.

The peritoneal exudate in all dogs in which there was no contamination was negative for bacteria and frequently remained so until one or two hours after death. Figure 2 clearly shows the difference between

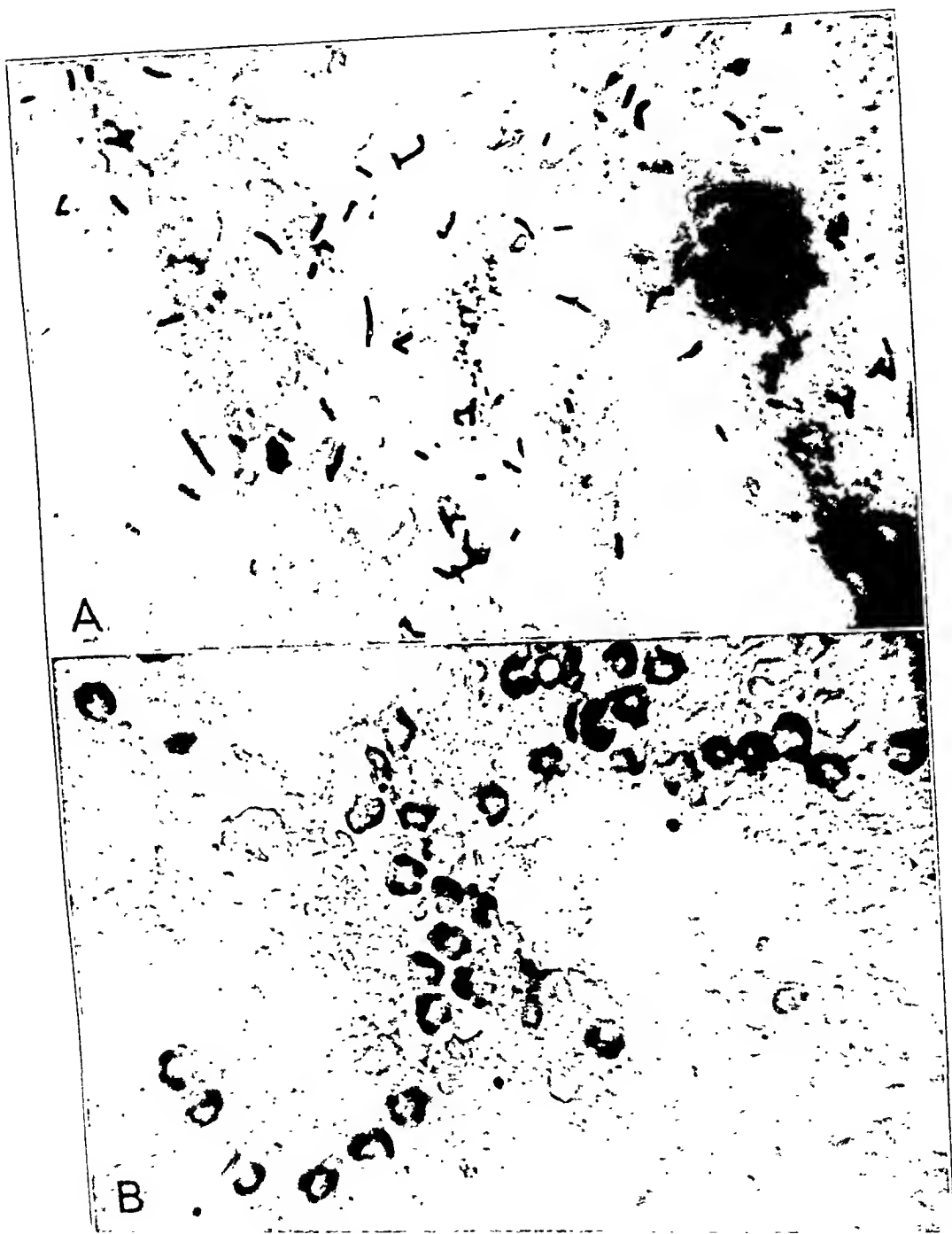


FIG. 2.—Photomicrographs of stained smears of samples of peritoneal exudate. *A* shows an example of bacterial peritonitis and *B*, an example of sterile peritonitis.



this type of sterile peritonitis and the typical bacterial peritonitis which occurs when bacteria are introduced into the peritoneal cavity. The difference becomes even more evident at autopsy. In the dog dying with a sterile peritoneum there was present a large quantity of thin blood-tinged fluid. The serous surfaces were fiery red. The liver and spleen were grossly normal and contained no gas, nor was gas present in the peritoneal cavity. There was marked hemorrhagic enteritis throughout the entire intestinal tract. In dogs in which death was associated with bacterial peritonitis, the picture at autopsy was similar except that the fluid present was turbid and foul and gas was present in varying amounts. The organisms found in the smears and cultures of the samples of exudate from these dogs were of many kinds, the anaerobic group of which at no time included *Cl. Welchii*. The anaerobic organisms present were invariably large, gram-positive, gas-forming saprophytes which exist in the normal tissues of the adult dog. In our experiments, these organisms have not produced a demonstrable exotoxin in vitro as compared with *Cl. Welchii* and other pathogenic anaerobes. As previously reported, by using accepted bacteriologic methods of cultivation and tests for the presence of bacterial exotoxins, we have been able in all cases to demonstrate these exotoxins in the filtrates of organisms known to produce them. We wish to point out that the intravenous injection of from 10 to 20 cc. of protein filtrates into small animals is not an accurate test for the presence of an exotoxin.

We do not deny that under certain conditions these nonpathogenic organisms cause death when they gain access to the peritoneal cavity. We have found, however, that when the broth portion of a growing culture of these saprophytes is injected intraperitoneally, even in amounts of 35 cc., no noticeable harmful effect results, but if the meat from the bottom of the tubes is injected together with the organisms, the dog dies promptly of bacterial peritonitis. *Cl. Welchii* gives a different result. In this instance 35 cc. of the clear broth culture is sufficient to cause death as a result of general toxemia, even though peritonitis is not found at autopsy. This indicates that in the presence of some unabsorbable material which can serve as a culture medium, even nonpathogenic organisms cause fatal peritonitis, but when these organisms can be rapidly absorbed from the peritoneum, no harm results unless the organisms are highly virulent.

There is much confusion in the literature concerning the proper classification of gram-positive, gas-forming anaerobes. There seems to be a tendency to use the terms "*Welch bacillus*" and "*gas bacillus*" promiscuously. The gas-forming organism described by Welch, however, is definitely pathogenic and is characterized by the formation of

an exotoxin. We have observed an instance of so-called endogenous infection caused by a "gas bacillus" complicating embolic gangrene of the arm. In this case the tissue of the upper part of the arm and of the axilla, the neck and the wall of the chest were distended with gas, but the patient showed no evidence of toxemia and responded promptly to amputation of the arm with drainage of the crepitant tissue. We believe that such cases cannot be classified accurately as infections caused by *Cl. Welchii*, but are more probably due to nontoxic gas-forming saprophytes growing in devitalized tissue. During the World War, Weinberg and Séguin<sup>8</sup> made the distinction between gas gangrene with toxemia, jaundice and hemolysis and putrefactive gangrene with little or no systemic effect. The toxic "gas gangrene" was caused by three known anaerobic organisms, each of which produced a demonstrable exotoxin. The three organisms were *Cl. Welchii*, *Clostridium oedematis* and *Clostridium oedematis-maligni*. The putrefactive gangrene was caused by a host of unclassified saprophytes which thrive in dead or devitalized tissue, and it was early found that débridement and drainage were sufficient to stop their growth. Infections by the three aforementioned pathogenic members of the genus are usually fatal unless proper specific treatment is available.

In dogs, the putrefactive type of gangrene can be produced by the intramuscular injection of highly toxic liver preparations which devitalize tissue and serve as a culture medium for the saprophytes commonly present there. Even when growing in the skeletal muscle tissue of the dog they do not usually cause death, recovery occurring when the infection is drained, either spontaneously or by surgical intervention. The death which results when these organisms gain access to the peritoneum has already been discussed.

We are not in sympathy with the thought that intraperitoneal injection of sterile, though toxic, material causes an idiopathic bacterial invasion of the peritoneal cavity during life. When, by suitable technic, the material was kept sterile, the peritoneum remained sterile even though the material was sufficiently toxic to cause death.

We do not wish to state that the dog's peritoneal cavity is always sterile under normal conditions. Recently the work of Roberts, Johnson and Bruckner<sup>9</sup> has been brought to our attention. These authors reported that in the bacteriologic study of the peritoneal fluid obtained during two hundred and nine laparotomies in human subjects, 80 per cent of the specimens contained different kinds of bacteria. They pointed

---

8. Weinberg, M., and Séguin, P.: *La gangrene gazeuse: bacteriologie, reproduction expérimentale, sérothérapie*. Paris, Masson & Cie. 1918.

9. Roberts, K.; Johnson, W. W., and Bruckner, H. S.: *The Aseptic Peritoneal Cavity: A Misnomer*. Surg., Gynec. & Obst. **42**:752 (Dec.) 1933

out that the peritoneal cavity was contaminated equally often in the absence of inflammatory reactions as in cases of active inflammation and concluded that the term "the aseptic peritoneal cavity" is a misnomer. We make no effort to compare these observations with the results we are reporting, except to state that we have obtained sterile cultures from samples of peritoneal exudate of dogs when, and only when, a technic was devised to avoid contamination from the abdominal wall.

Our cultural methods, as previously reported, conform to the accepted methods of study of anaerobic bacteria. We have consistently produced the growth of many kinds of bacteria when the organisms gained access to the medium. We see no reason to question our results on this basis. A plausible explanation for the conflict in our results as compared to those reported by Andrews seems obvious. We have found that routine aseptic surgical technic is inadequate for bacteriologic studies in the dog.

#### CONCLUSIONS AND SUMMARY

1. The tissues of living dogs contain an anaerobic flora which is composed of several strains of unclassified, putrefactive, gas-forming saprophytes. We did not find *Cl. Welchii*.
2. One hundred grams of fresh, finely ground dog liver sterilized by autoclaving when injected intraperitoneally, does not cause death unless contamination occurs during or after injection.
3. When fresh liver containing its normal flora is placed in the peritoneal cavity, or when sterile suspensions of liver injected intraperitoneally become contaminated, death occurs and is associated with bacterial peritonitis.
4. One hundred grams of finely ground liver incubated for twenty-four, forty-eight or seventy-two hours and sterilized by autoclaving when injected intraperitoneally in an uncontaminated state causes death promptly in the dog. Death is not caused by bacterial growth in the peritoneal cavity.
5. The intraperitoneal injection of 5 cc. per kilogram of body weight of a 10 per cent sterile solution of the two bile salts is fatal in a few hours. Death is not caused by a bacterial growth in the peritoneal cavity.
6. Neither the sterile liver nor the bile salts per se cause an invasion of the peritoneal cavity by *Cl. Welchii* or by any other bacteria.
7. The various incubated preparations of liver and the sterile bile salts cause an intense irritation of the peritoneal surfaces, with much

extravasation of blood and fluids, and we believe the death of the dog to be associated with shock.

8. We have reported a method which has proved satisfactory in our hands for removing uncontaminated samples of peritoneal exudate from the dog's peritoneal cavity.

This work has been done under the supervision of Dr. W. D. Gatch. Assistance has been given us by Dr. Thurman B. Rice of the department of bacteriology and pathology and by Mr. Fred A. Miller and Mr. Galen Boring of the biologic department of the Eli Lilly Research Laboratories.

# DEVELOPMENT AND TREATMENT OF PEPTIC ULCER

## AN EXPERIMENTAL STUDY

FRED R. HARPER, M.D.  
Fellow in Surgery, the Mayo Foundation  
ROCHESTER, MINN.

Numerous methods have been devised for the experimental production of peptic ulcer in animals. In these experiments, spontaneous experimental peptic ulcer was produced in an intestinal fistula that extended from a gastric pouch to the abdominal wall. This method permits the investigation of phases of the problem which have not heretofore been touched on. As the ulcers were completely removed from the main gastro-intestinal tract, many confusing factors could be eliminated. Furthermore, the ulcers were easily accessible, so that various types of treatment could be applied directly to their surface.

In a preliminary report I<sup>1</sup> outlined the factors that were responsible for the development of such an ulcer, the changes in the secretion in the pouch and a method of preventing or healing the ulcer. In this paper a more complete report will be made concerning the development of the ulcers, concerning mucosal susceptibility to the formation of the ulcers and concerning methods of treatment.

### METHOD

Dogs were used in all of the experiments and were prepared according to the technic of Goldberg and Mann.<sup>2</sup> The operation was performed in two stages. The first stage consisted in resecting a loop of intestine from 10 to 15 cm. long. Intestinal continuity was reestablished by an end-to-end anastomosis. The distal end of the resected loop was then sutured to an opening in the stomach, and the proximal end was brought out through a stab wound in the abdominal wall. By arranging the transposed loop in this way, the peristaltic waves traveled toward the stomach, thus preventing leakage of the secretion from the pouch. The second stage was performed from three weeks to six months later, and consisted in dividing the stomach so that the portion of it that was drained by the intestinal fistula formed a gastric pouch (fig. 1).

---

Abridgment of a thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Surgery. The work was done in the Division of Experimental Medicine.

1. Harper, F. R.: Development of Experimental Peptic Ulcer: Changes in Acidity and Treatment, *Proc. Staff Meet., Mayo Clin.* 7:318 (June 1) 1932.

2. Goldberg, S. L., and Mann, F. C.: Preparing Pouches of the Fundus of the Stomach, *Ann. Surg.* 94:953 (Nov.) 1931.

In order to determine the importance of gastric secretion in the development of spontaneous ulcer and the resistance of the various levels of the intestinal mucosa to the formation of ulcer, various preparations were made, using different parts of the stomach in combination with different levels of the intestine. Thus, pouches made from the cardiac, the pyloric or the fundic portion of the stomach were drained by fistulas from the ileum. Since the fundic portion of the stomach secretes the most acid, fistulas made from the jejunum and the duodenum were also used in draining the fundic pouches.

Three additional types of preparation were made that require special mention. Each of two dogs was prepared with a double fistula made from the ileum. This was arranged so that peristalsis in one of the fistulas would travel toward the stomach, whereas, in the other it would be directed away from the stomach. The pouch was made from the fundus of the stomach and included both of these

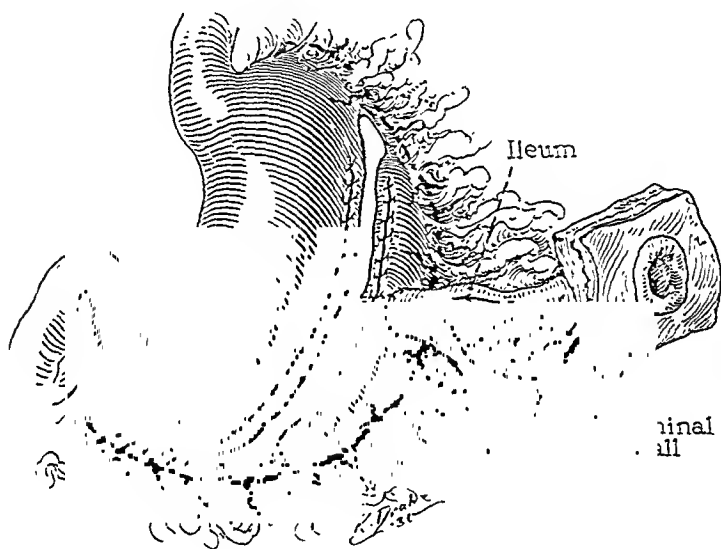


Fig. 1.—Formation of an isolated gastric pouch, second operation.

fistulas. In one dog a Pezzer catheter was inserted through the fistula into the fundic pouch, so that the mushroom-like end impinged on the walls of the pouch. This catheter was kept in place continuously after the second stage so that all of the secretion which left the pouch was carried out by the catheter and did not come in contact with the mucosa of the fistula. The secretion was collected in a balloon attached to the catheter. Another dog was prepared with a pouch made from the fundus of the stomach and a fistula from the jejunum. In this dog the nerve supply to the fistula was destroyed by stripping the mesenteric vessels.

In the case of each animal the weight was recorded and bleeding from the fistula or other changes were noted at regular intervals. These data were found to be important in determining the time when the ulcer began to develop. Studies of the secretion from the pouch were made every third or fourth day as the ulcer developed. The secretion was examined in a routine manner. The dog fasted for twenty hours before a series of observations was started. After a specimen was taken the dog was fed 100 Gm. of diced raw meat. The contents of the pouch

were then withdrawn at two hour intervals by means of a soft rubber catheter inserted into the pouch through the fistula. The dog was replaced in its cage between observations. These two hour specimens were taken over periods of eight, twelve or twenty-four hours. The amount and character of each specimen were recorded, and the  $pH$ , the free and the combined acidity in terms of tenth-normal sodium hydroxide per hundred cubic centimeters, and the number of milligrams of total chlorine per hundred cubic centimeters of gastric secretion were determined.

Three substances were tried in treating the ulcers. Sodium bicarbonate was given by mouth and also injected into the pouch. Gastric mucin was introduced into the pouch in an attempt to heal the ulcer or to prevent its formation. Finally, an emulsion was prepared, using gelatin, acacia, olive oil and lecithin. Twenty cubic centimeters of this emulsion was introduced into the pouch twice daily during the time the ulcer was being treated.

Necropsy was performed on each animal, and gross and microscopic studies were made of all specimens. A sufficient number of animals was used to permit definite conclusions to be drawn.

#### RESULTS

A study of the results brought out several points in regard to the factors responsible for the development of this type of experimentally produced ulcer. In the first place, in no instance did an ulcer develop after the first stage of the operation, even though the animal was kept for a long time and catheters were repeatedly passed through the fistula. It was thus possible to rule out certain factors such as trauma, a faulty supply of blood and so forth.

When the fundus of the stomach was used in making the pouch, free acid was found in the secretion of the pouch and an ulcer formed in the fistula in each of the animals. However, if the cardiac or the pyloric portion of the stomach was used in making the pouch, free acid was not present in the secretion of the pouch and an ulcer did not form in the fistula. Furthermore, when the fistula was protected by constantly draining the secretion from the pouch through a Pezzer catheter, an ulcer did not form. These observations illustrate the significance of the chemical or acid factor in the development of ulcers.

As has been mentioned, each of two dogs was prepared with two fistulas draining a fundic pouch. In these dogs an ulcer did not develop in either fistula. In one of them, after more than ample time had been allowed for an ulcer to develop, one of the fistulous loops was removed and the abdomen was explored to make sure no ulcer existed in the other loop. Two weeks after the fistulous loop was removed, a perforating ulcer was found at necropsy in the remaining loop of the intestine. It may be that mechanical factors contribute to the development of such ulcers and that a second draining fistula eliminates these factors.

The series in which a loop of the intestine was used in combination with the fundic portion of the stomach illustrated the varied susceptibility of the mucosa of different regions of the intestine to the formation

of ulcer. When a portion of the ileum was used, the average length of time before perforation occurred was twenty-three days; when the jejunum was used, the average time was seventy-one days, and when the duodenum was used, ulcers formed but did not perforate. It was thus fairly well established that the vulnerability of the mucosa to the formation of ulcer becomes greater as the distance from the stomach is increased.

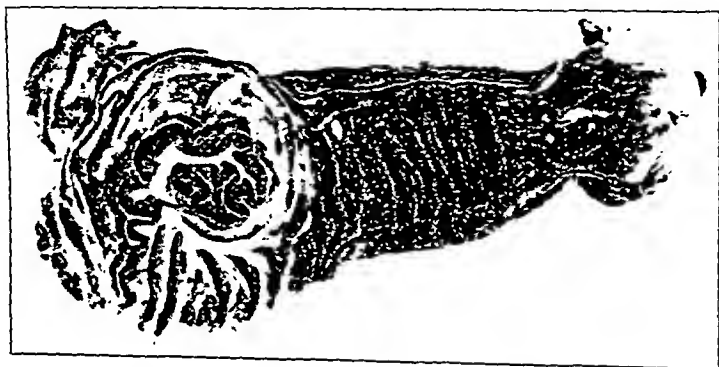


Fig. 2.—Ulcer in a fistula made from the ileum. Note the lack of resistance of the ileal mucosa to the formation of ulcer and that the ulcer does not begin at the line of suture.



Fig. 3.—Chronic nonperforating ulcer in a fistula made from the duodenum.

There are several other points that should be mentioned in regard to the preparations. The size of the pouch apparently had no effect on the rate of development of the ulcer or on its size. Also, the length of the intestinal loop that was used in making the fistula did not influence the formation of the ulcer. In each case the ulcer was situated in the fistula, about 1 cm. from the line of suture that joined the fistula to the pouch. The ulcers which occurred in the fistulas made from the ileum were of the acute perforating type (fig. 2), whereas the ulcers in the fistulas made from the jejunum or from the duodenum resembled



chronic duodenal ulcers in man, as to both gross and microscopic appearance. (fig. 3). Although the ulcers were entirely separate from the main part of the gastro-intestinal tract and did not come in contact with food, they had a very definite effect on the animals, the most striking effect being the rapid loss in weight, which amounted to from 1 to 6 Kg. On the other hand, the dogs actually gained weight on the same regimen when ulcers were prevented from forming. In addition to the loss of weight, definite symptoms developed as the ulcer became advanced, chief among which were loss of appetite and vomiting after eating. In the later stages the chlorides in the blood were reduced to from 280 to 300 mg. per hundred cubic centimeters. When a dog with a well developed ulcer was given 200 cc. of 10 per cent dextrose in 1 per cent saline

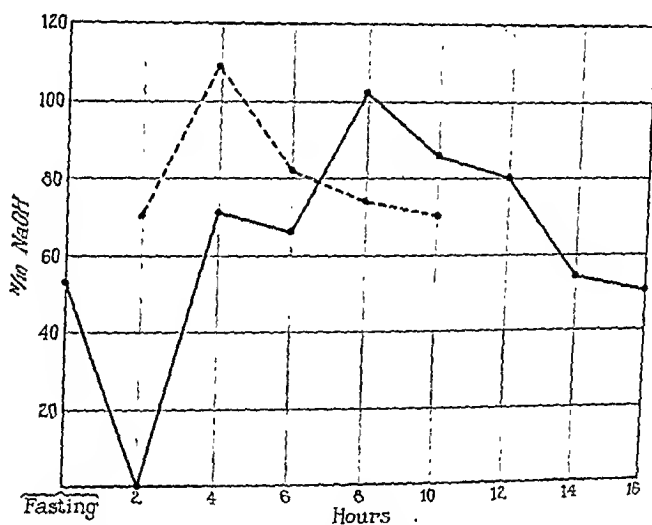


Fig. 4.—The effect of sodium bicarbonate on the acidity of the secretion from the pouch. The broken line represents the values for total acidity two days before sodium bicarbonate was given; the solid line, the values obtained after the administration of 1 Gm. of sodium bicarbonate per kilogram with a test meal.

solution or 200 cc. of whole blood, the condition improved temporarily. In several instances the dog regained from 0.5 to 1 Kg. in weight.

The situation of the ulcers and the ease with which they could be approached made them particularly adaptable to the application of various types of treatment. Sodium bicarbonate was introduced into the pouch by means of a syringe and also given by mouth with the test meal. In either case it had the effect of depressing the acidity for from two to four hours, after which time the acidity returned to its former level and remained elevated for from fourteen to sixteen hours (fig. 4). Mucin introduced into the pouch in doses of 8 Gm. twice daily stimulated the secretion of acid and did not prevent the formation of an

ulcer. However, these experiments were made before the investigations of Rivers, Vanzant and Essex<sup>3</sup> had been carried out, so it is possible that an impure product was used. The ulcer that formed in the presence of mucin was of a type different from the others; it was much larger, but it did not have the same tendency to perforate, and bleeding did not occur.

A method of treatment which was suggested by Mann and Bollman<sup>4</sup> was successful in preventing the formation of ulcers and also in healing them. The preparation used consisted of: gelatin, 100 Gm.; acacia, 150 Gm.; water, 500 cc., and olive oil, 300 cc. The gelatin, acacia and water were heated together over a water bath until dissolved. The lecithin was dissolved in some of the olive oil over an open flame, and

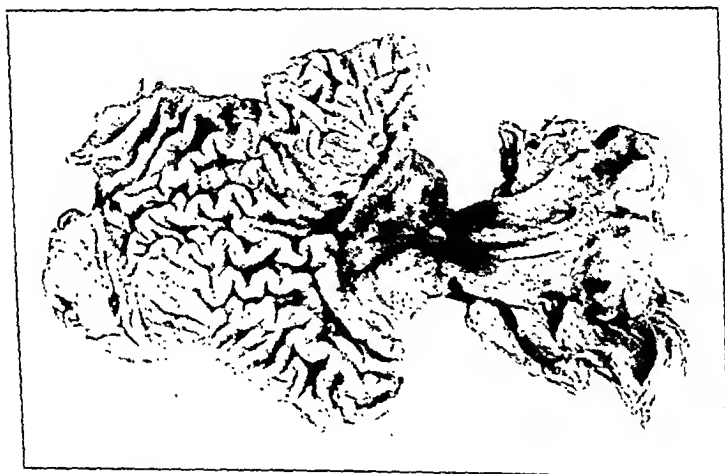


Fig. 5.—Healing of an ulcer subsequent to three weeks' treatment with the emulsion. Note the small bud of granulation tissue in the center.

the oil was then mixed into the gelatin, acacia and water so that a thick emulsion resulted. In treating an ulcer, the mixture was heated until it would flow, and from 20 to 30 cc. was inserted into the pouch twice daily by means of a syringe. The emulsion was markedly tenacious and did not stimulate the secretion of acid. It left the stomach intact in about six hours.

Five dogs were treated with this emulsion. In one of the dogs the treatment was started immediately following the second stage of the

3. Rivers, A. B.; Vanzant, F. R., and Essex, H. E.: The Dangers of Using Impure Mucin in the Treatment of Peptic Ulcer, *J. A. M. A.* **98**:1156 (April 2) 1932.

4. Mann, F. C., and Bollman, J. L.: Experimentally Produced Peptic Ulcers: Development and Treatment, *J. A. M. A.* **99**:1576 (Nov. 5) 1932.

operation, and an ulcer did not develop. In the others, treatment was not started until there was definite evidence of the formation of an ulcer, such as bleeding, loss of weight and so forth. In the dogs in which an ulcer had already formed, healing of the ulcer was effected in about three weeks by continuous treatment, and healing was accompanied by an apparent decrease in the acidity of the secretion from the pouch and also by an increase in the appetite and in the weight of the animal.

Pathologic changes in this healing process were the same as in the healing process described by Mann.<sup>5</sup> In early stages the defect was



Fig. 6.—Section of a healed ulcer which had been treated with the emulsion. Note the atypical mucosa and the defect in the muscularis, the two most important histologic characteristics of a healed ulcer.

filled in with a bud of granulation tissue, and a single layer of mucosal cells grew over this bud. As the healing process continued, the bud of granulation tissue was pinched off and the area became covered with newly formed mucosa which finally developed into typical intestinal villi. The layers of muscle which were destroyed did not regenerate, but the defect was filled in by fibrous scar tissue which remained as evidence of the previously existing ulcer (figs. 5 and 6).

5. Mann, F. C.: Production and Healing of Peptic Ulcers: An Experimental Study, *Minnesota Med.* 8:638 (Oct.) 1925.

## COMMENT

A method has been described by which a type of chronic peptic ulcer can be produced experimentally with great uniformity. The method consists in making a pouch of fundic mucosa and draining it with a loop of intestine. The ulcer develops in the intestinal loop just distal to the stoma of the pouch. These ulcers differed from peptic ulcers found in man in that they were entirely separate from the main gastro-intestinal tract; their isolation from the main gastro-intestinal tract made them readily accessible, facilitated the study of their development and showed the effect of different methods of treatment.

A number of factors have been considered by various workers as significant in the etiology of peptic ulcer. Many of these factors can be eliminated in regard to this type of ulcer. In the first place, a faulty supply of blood did not play a part, as shown by the fact that an ulcer never developed after the first stage when the intestinal loop was isolated and anastomosed to the stomach, although by this operation the supply of blood to the fistula was impaired. During the second operation, in which the pouch was made, the supply of blood to the fistula was not affected in any way. In the second place, operative and external traumas were not factors of importance in producing these ulcers, because an ulcer did not develop even when a catheter was passed repeatedly following the making of the fistula. It is not likely that infection was a factor in the development of these ulcers, although, the part played by infection is difficult to evaluate. That faulty suture material was not of etiologic significance is indicated by the fact that the ulcers started not at the line of suture but about 1 cm. from it.

Mann and Williamson<sup>6</sup> and also Morton,<sup>7</sup> McCann,<sup>8</sup> Ivy and Fauley<sup>9</sup> and, more recently, Matthews and Dragstedt<sup>10</sup> have referred to three factors as significant in the development of peptic ulcer: the chemical factor, the mechanical factor and the susceptibility of the mucosa; all of these seemed to be of significance in the production of the experimental ulcers described. In these experiments the chemical

6. Mann, F. C., and Williamson, C. S.: The Experimental Production of Peptic Ulcer, *Ann. Surg.* **77**:409 (April) 1923.

7. Morton, C. B.: Observations on Peptic Ulcer, *Ann. Surg.* **87**:401 (March) 1928.

8. McCann, J. C.: Experimental Peptic Ulcer, *Arch. Surg.* **19**:600 (Oct.) 1929.

9. Ivy, A. C., and Fauley, G. B.: Factors Concerned in Determining the Chronicity of Ulcers in the Stomach and Upper Intestine, *Am. J. Surg.* **11**:531 (March) 1931.

10. Matthews, W. B., and Dragstedt, L. R.: The Etiology of Gastric and Duodenal Ulcer, *Surg., Gynec. & Obst.* **55**:265 (Sept.) 1932. Dragstedt, L. R., and Vaughn, A. M.: Gastric Ulcer Studies, *Arch. Surg.* **8**:791 (May) 1924.

factor was demonstrated clearly. Other conditions being constant, an ulcer would not develop in the absence of free acid. Thus, if the cardiac or the pyloric portion of the stomach was used in making the pouch, no free acid was secreted and no ulcer developed. Likewise, if the intestinal mucosa was protected from the acid secretion by the use of a Pezzer catheter, an ulcer did not develop.

The mechanical factors which contribute to the formation of ulcers are difficult to evaluate. However, it seemed significant that in these animals the experimental ulcer developed uniformly at a point at which the secretion, emerging from the pouch into the fistula, met the obstruction in the fistula which prevented free drainage and thus caused a welling up of secretion in the first part of the fistula. It is also significant that in pouches drained by two fistulas an ulcer did not develop until one of the fistulous loops was removed. It may be that mechanical forces are important when gastric secretion is kept constantly in contact with exposed mucosa.

The third factor, mucosal susceptibility, which has also been emphasized by Matthews and Dragstedt,<sup>10</sup> was clearly brought out by the greater rapidity with which the ulcers formed when lower levels of the intestinal tract were used in making the fistulas. This illustrates a point that should be of significance in the etiology of gastrojejunal ulcers, namely, that the vulnerability of the mucosa to the development of ulcers increases as the distance from the pylorus becomes greater.

Although the ulcer was not situated in the main part of the gastrointestinal tract and did not come in contact with ingested food, a progressive and marked loss of weight occurred in each dog in which ulcer developed. This loss of weight was associated with loss of appetite, vomiting, dehydration and reduction of chlorides in the blood. A temporary gain in weight could be brought about by intravenous injections of saline solution or by transfusions. While carefully controlled experiments were not carried out to prove the point, it is possible that the loss of weight and other symptoms observed were due to a disturbance in the chemistry of the blood resulting from a loss of chlorides.

The method used in treating the ulcers was based on the hypothesis that substances which would coat the surface of the ulcer and protect it from the gastric secretion would promote healing under this coating. The preparation used was an emulsion of gelatin, acacia, olive oil and lecithin. The gelatin was used to hold the mixture together and make it more tenacious. The acacia supplied the adherent or protective qualities. The vegetable oil was used for three purposes: first, for its depressing effect on gastric secretion, as illustrated by the work of Pavlov<sup>11</sup> and others; second, because it leaves the stomach very slowly, as shown by

---

11. Pavlov, I. P.: *The Work of the Digestive Glands*, ed. 2, London, C. Griffin & Company, 1910.

Gianturco,<sup>12</sup> and third, because it has a protective action. The lecithin was used to make the emulsion smoother and also for its protective effect. The method described was successful in treating this type of ulcer in five experiments. Ulcers developed in all of the untreated animals, whereas in the five dogs that were treated with the emulsion, ulcers did not develop.

The fact that healing and destruction occur simultaneously in peptic ulcers is known. The purpose of using the method described was to protect the surface of the ulcer from the gastric secretion for a sufficient time to permit the healing process to go on to completion. Although there were not enough experiments carried out to prove the actual value of the method, the experiments did suffice to bring out the fact that an ulcer will heal in about three weeks if its surface is afforded sufficient protection. Neither sodium bicarbonate nor the preparation of mucin used was effective in preventing or healing these ulcers.

Pathologically, the specimens presented all of the characteristics typical of the various stages of the healing process as described by Mann for experimental ulcers and by Caylor<sup>13</sup> for ulcers of man.

#### SUMMARY

A method has been described for producing an experimental peptic ulcer in a loop of intestine forming a fistula from an isolated gastric pouch to the abdominal wall. An ulcer formed in each of the dogs in which the fundus of the stomach was used in making the pouch. Several facts were brought out in these experiments. It was shown that a combination of three factors was responsible for the development of these ulcers: the chemical factor, the mechanical factor and the factor of mucosal susceptibility. The chemical action of the gastric secretion was found to be of prime importance. The increasing vulnerability of the intestinal mucosa to the formation of ulcer as the distance from the stomach increased was demonstrated. The mechanical factor probably played a part, for the ulcer developed at a point where the gastric secretion was held constantly in contact with the exposed intestinal mucosa. It was found that an ulcer in an isolated gastric

---

12. Gianturco, Cesare: Some Mechanical Factors of Gastric Physiology: Study I. The Empty Stomach and Its Various Ways of Filling. The Pressure Exerted by the Gastric Walls on the Gastric Content. The Physical Changes Occurring to the Foodstuff during Digestion, *Am. J. Roentgenol.* **31**:735 (June) 1934; Some Mechanical Factors of Gastric Physiology: Study II. The Pyloric Mechanism. The Effect of Various Foods on the Emptying of the Stomach, *ibid.* **31**:745 (June) 1934.

13. Caylor, H. D.: The Healing of Gastric Ulcer in Man, *Ann. Surg.* **83**:350 (March) 1926.

pouch has the same effect in causing loss of appetite, vomiting and loss of weight as does an ulcer in the main gastro-intestinal tract.

A preparation consisting of an emulsion of gelatin, acacia, olive oil and lecithin, introduced into the pouch twice daily, was effective in the healing of these experimental ulcers and prevented their formation. The pathologic changes that occurred in the healing of the ulcers were found to be similar to the changes which occur in peptic ulcers in man. The method of treatment was considered important because it brought out the fact that an ulcer will heal in about three weeks if its surface is adequately protected from the gastric secretion. The emulsion used in treating the ulcers has been considered only from the experimental point of view, and no conclusion can be drawn regarding its possible clinical application.

# LYMPHOSARCOMA

A CLINICAL, PATHOLOGIC AND RADIOTHERAPEUTIC STUDY,  
WITH A REPORT OF THIRTY CASES

MAX CUTLER, M.D.

Consultant in Tumors, Veterans' Administration Facility, and Director,  
Tumor Clinic, Michael Reese Hospital

CHICAGO

The purpose of this investigation was to correlate the clinical, roentgenologic and pathologic observations on a group of patients suffering from lymphosarcoma, with special emphasis on the differential diagnosis and the radiosensitivity of the associated mediastinal lesions.

In order to be of value a study of this type should fulfil several conditions: The clinical observations must be controlled by pathologic data; the ultimate fate of the patient must be known, and in case of death there must be a control by autopsy. All these conditions are fulfilled in this investigation.

The material on which this analysis is based consists of 30 cases of microscopically proved lymphosarcoma. The end-result is known in every case, constituting 100 per cent follow-up, and an autopsy was performed on each of the 13 patients who died in the hospital.

One of the most interesting and largely unexplained features of neoplastic diseases is the marked variations that are noted in the rate of progress and extension. This renders it highly important that we become familiar with the natural history of the different types of tumor and with their behavior under various therapeutic methods. Because of this circumstance, extensive clinical and pathologic material offers the opportunity to study extreme variations in the disease which more limited material usually fails to disclose.

## AGE INCIDENCE

The patients in the Veterans' Administration Facility do not represent a random sampling of the population, but constitute a rather selected group, discharge from military service being the primary criterion for admission. Because of this the age incidence is not necessarily a true picture of the general incidence of the disease, but in spite of this cir-

---

From the Cancer Research Unit, Veterans' Administration Facility, Hines, Ill.

Published with the permission of the Medical Director of the Veterans' Administration Facility, who assumes no responsibility for the opinions expressed or the conclusions drawn.



cumstance the age of onset of symptoms is of some interest; figure 1 indicates the age distribution in this series. The minimum age at the onset of symptoms was 30 years and 4 months, the maximum age, 61 years and 3 months, and the mean age, 43.2 years.

#### PATHOLOGY

Kundrat<sup>1</sup> was the first to give a clear description of lymphosarcoma as a growth arising from a group of lymph nodes, or, more rarely, from a single node or from lymphoid tissues such as are encountered in the tonsils, the pharynx or the intestinal tract. The lesion, composed of a reticulum in which lymphoid cells abound, destroys the capsule of the

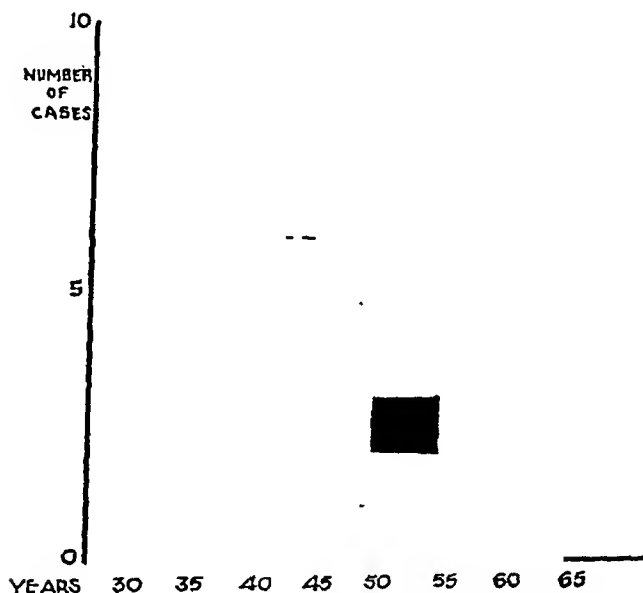


Fig. 1.—A chart showing the age at the onset of symptoms.

node and invades the adjacent lymph nodes. The separation of lymphosarcoma from the leukemias and pseudoleukemias was accomplished by Kundrat and Paltauf.

Metastatic tumors in distant organs are often observed. The disease tends, however, to grow through the lymph channels, with generalized involvement of groups of lymph nodes. The disease is sometimes limited to one region, such as the mediastinal lymph nodes, the retroperitoneal lymph nodes or the gastro-intestinal tract.

According to Ewing,<sup>2</sup> lymphosarcoma is to be distinguished from other forms of lymphoma by its local destructive capacity and by the

1. Kundrat: Ueber Lympho-Sarkomatosis, Wien. klin. Wchnschr. 6:211, 1893.

2. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 1093.

formation of true metastases in different organs arising in a chain of lymph nodes. The tumors rapidly become bulky, infiltrate the surrounding tissue and tend to cause ulceration and necrosis of the skin and of the mucous membranes.

Histologically, lymphosarcoma is generally divided into two groups: (1) reticulum cell sarcoma or large round cell lymphosarcoma arising from the reticulum, and (2) malignant lymphocytoma arising from the lymphocytes. Ewing was of the opinion that in the great majority of cases the two varieties retain their separate identity and arise under different clinical conditions.

## OBSERVATIONS AT AUTOPSY

Table 1 indicates the pathologic observations on 13 patients with lymphosarcoma who were examined at autopsy, showing various tissues and organs which were involved.

TABLE 1.—*Involvement of Tissues and Organs Observed at Autopsy*

	No. of Cases		No. of Cases
Skin and subcutaneous tissues.....	4	Liver.....	9
Cervical lymph nodes.....	7	Spleen.....	2
Axillary lymph nodes.....	6	Pancreas.....	6
Inguinal lymph nodes.....	5	Kidney.....	6
Peribronchial lymph nodes.....	9	Thymus.....	3
Retroperitoneal lymph nodes.....	8	Stomach.....	1
Mesenteric lymph nodes.....	3	Diaphragm.....	1
Lungs.....	1	Peritoneum.....	3
Pleura.....	7	Wall of the chest.....	1
Pericardium.....	4	Pharynx.....	1
Heart.....	2	Accessory nasal sinuses.....	1

## CLINICAL VARIETIES

A study of this group of cases indicates that the following division into various clinical groups can be established:

1. Lymphosarcoma with generalized adenopathy and no special localization.<sup>3</sup>
2. Lymphosarcoma associated with localization in the tonsil, the pharynx or the base of the tongue.
3. Lymphosarcoma associated with pronounced involvement of the retroperitoneal lymph nodes.
4. Lymphosarcoma, with localization in the rectum.
5. Lymphadenoma.
6. Lymphosarcoma probably arising in the thymus and other thymic tumors of uncertain histogenesis.

3. Nine cases of a total of 30 fall into this category. Aside from the autopsy observations included in table 1 there are no points of special interest in the group.

## LYMPHOSARCOMA WITH LOCALIZATION IN THE TONSIL, THE PHARYNX OR THE BASE OF THE TONGUE

In the cases of 100 patients with nasopharyngeal tumors treated at the Memorial Hospital, New York, Ewing<sup>4</sup> reported the following pathologic diagnoses: transitional cell carcinoma, 47 cases; squamous cell carcinoma, 30; lymphosarcoma, 15; lympho-epithelioma, 11; adenoid-cystic epithelioma, 4, and malignant adenoma, 3. Thus, lymphosarcomas constituted 15 per cent of the group of nasopharyngeal tumors. The relative frequency of lymphosarcoma associated with lesions of the tonsils, the pharynx and the cervical lymphatic glands has suggested to some that an infectious agent is the etiologic factor (Chiari).

CASE 1.—A. W. was a man aged 70, in whom the first sign of disease was enlargement of the right submaxillary lymphatic glands. The lesions were removed and were proved histologically to be reticulum cell lymphosarcoma. One year later there developed an abdominal tumor, and at an exploratory operation a large retroperitoneal mass attached to the right kidney was discovered and removed with the kidney. The histologic structure was similar to that found in the submaxillary lymphatic glands. Six months later, or eighteen months after the first sign of disease, an ulcerative lesion 2 by 2 cm. was noted on the right side of the base of the tongue. A biopsy on this lesion showed lymphosarcoma, the structure being similar to that discovered in the submaxillary glands and the retroperitoneal mass. Radium treatment over the mass in the tongue resulted in its complete disappearance. At the time of writing there is no further clinical evidence of the disease.

Lymphosarcoma associated with lesions of the tonsil may be unilateral or bilateral. It frequently grows to large dimensions and is seen as a bulky tumor which does not ulcerate until late. The cervical lymphatic glands are almost always involved in the early stage of the disease. In rare cases the disease is localized to the tonsil and the regional lymphatic glands, and adequate irradiation results in the disappearance of the lesion, the patient sometimes remaining well for prolonged periods. Minot and Isaacs<sup>5</sup> reported 1 patient well after six years. Others have reported long survivals. In most instances the disease in the tonsil or nasopharynx and the associated cervical lymphatic glands constitutes only a local expression of generalized lymphosarcomatosis, as exemplified in the 5 cases to be reported. Clinically and histologically lymphosarcoma of the tonsil and nasopharynx can be easily confused with lympho-epithelioma and transitional cell carcinoma, all three lesions being highly, and equally, radiosensitive. In many cases the similarity is so striking that a differential diagnosis is exceedingly difficult.

4. Ewing, J.: Radiosensitivity, *Radiology* **13**:313 (Oct.) 1929.

5. Minot, G. R., and Isaacs, R.: Lymphoblastoma: Aspects Concerning Abdominal Lesions Especially Their Production of Early Symptoms, *Am. J. M. Sc.* **172**:157 (Aug.) 1926; Lymphoblastoma (Malignant Lymphoma): Age and Sex Incidence, Duration of Disease, and Effect of Roentgen Ray and Radium Irradiation and Surgery, *J. A. M. A.* **86**:1185 (April 17); 1265 (April 24) 1926.

CASE 2.—A. K., a man aged 40, had generalized adenopathy which was first noted in the left cervical region in January 1932. Dyspnea and loss of weight developed four months later. A biopsy on a node showed lymphosarcoma. Physical examination revealed generalized enlargement of the lymph nodes, and roentgenologic examination showed a widening of the mediastinal shadow. There was marked edema of the lower extremities. There were numerous cutaneous and subcutaneous, firm, movable nodules in the scalp. In the left tonsillar fossa was a mass pushing the anterior tonsillar pillar forward and extending downward toward the epiglottis. The lesion failed to respond to irradiation. The patient's general condition grew rapidly worse, and he died soon after admission. At autopsy it was found that the entire lymphatic system was involved. All the lymph nodes were invaded, and there were metastases in the spleen, the liver and the kidneys.



Fig. 2 (case 4).—*A* shows large masses in the supraclavicular and cervical areas before treatment. There was also a nasopharyngeal growth. *B* shows the same areas after treatment. The disease recurred promptly, and the patient died two months later.

CASE 3.—F. K., a man aged 43, was admitted to the hospital on May 13, 1932, with a history that three months previously he first noted soreness of the throat and difficulty in swallowing, followed by the appearance of a mass in the left cervical region. Examination revealed a mass in the posterior nasopharynx, with metastasis to the right cervical lymph nodes. Microscopic examination of a biopsy specimen revealed reticulum cell lymphosarcoma. External irradiation resulted in a moderate regression of the primary and metastatic lesions. In July 1932, the patient was readmitted to the hospital with recurrence and extension to the left middle ear, resulting in deafness. External irradiation with the radium "bomb" resulted in marked improvement of the local lesion and in disappearance of the pain and deafness. The patient was readmitted in October 1932, with renewed activity of the primary lesion, paralysis on the right side of the face, extreme weakness and dyspnea. The patient died eleven days later of terminal

bronchopneumonia. Autopsy revealed that the nasopharyngeal lesion had extended to all the accessory sinuses. No visceral metastases were found. Microscopically the lesion was a reticulum cell lymphosarcoma.

CASE 4.—J. Y., a man aged 61, first noticed a small gland in the right submaxillary region in November 1932, followed by rapid enlargement of the cervical glands on both sides. About the same time the patient became aware of a growth in the left nostril which interfered with his breathing. Examination revealed a large mass in the posterior nasopharynx and extensive bilateral submaxillary, cervical, supraclavicular, axillary and inguinal adenopathy (figs. 2 and 3). A biopsy specimen from the nasopharyngeal mass showed reticulum cell lymphosarcoma (fig. 4).

Roentgen therapy resulted in rapid regression and the disappearance of the nasopharyngeal growth and the cervical adenopathy. The patient was able to breathe easily, his general condition improved markedly, and he gained 10 pounds (4.5 Kg.). One month later the right axillary and right infraclavicular masses

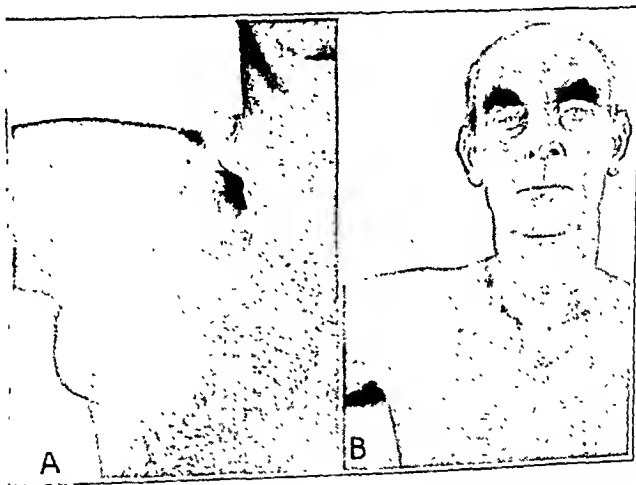


Fig. 3 (case 4).—*A* shows masses in the infraclavicular and axillary areas before treatment; *B* shows the same areas after treatment.

recurred, and a second cycle of radiation was administered with moderate regression. One month later the disease recurred and became widely disseminated, and the patient died at home. Autopsy was not performed.

CASE 5.—L. F., a man aged 32, was first admitted to the hospital April 6, 1932. Two and one-half years previously a growth was removed from the nose, which recurred three months later. There was moderate obstruction to breathing but no pain. Examination revealed the right nares to be filled with a bulky, soft tumor. There was swelling of the right nares, with bulging of the lateral wall. The growth extended through the soft palate, filled the nasopharynx and involved the right antrum (fig. 5). There was extensive cervical adenopathy. Examination of the biopsy specimen revealed lymphosarcoma (fig. 6). External irradiation resulted in a marked reduction in the size of the tumor. Six months later the patient was readmitted to the hospital with a swelling over the right antrum and a recurrence of the tumor in the nasopharynx. External irradiation resulted in marked regression. The patient was readmitted in March 1933 with exophthalmos

of the right eyeball, recurrence in the nasopharynx and cervical adenopathy on the right side. At the time of writing the patient is totally blind.

CASE 6.—J. B., a man aged 38, had a swelling on the left side of the neck which first appeared in January 1931. There was a rapid increase in the size of the mass, accompanied by severe pain. Examination in May 1931 revealed enlargement and ulceration of the left tonsil. The tonsil was removed, and a microscopic diagnosis of chronic inflammation was made. In October 1931, enlargement of the

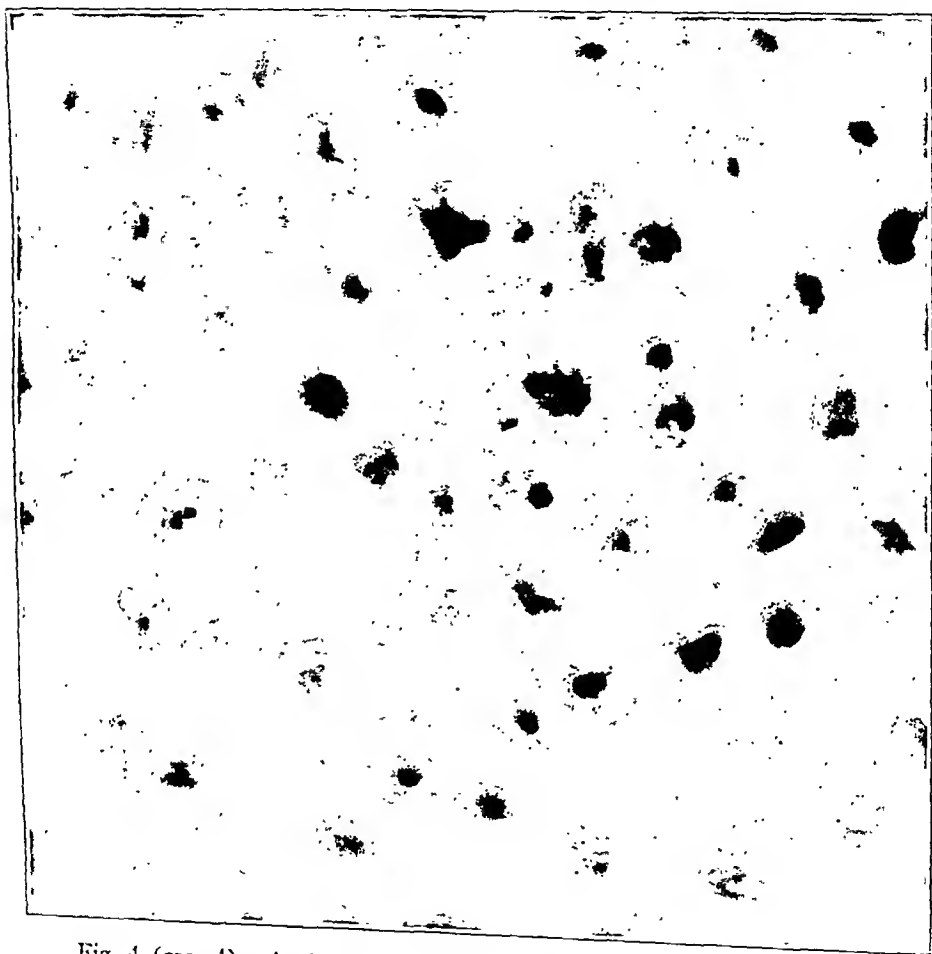


Fig. 4 (case 4).—A photomicrograph of a section of a reticulum cell lymphosarcoma of the nasopharynx.

cervical nodes on the left side was noted. Microscopic examination of a biopsy specimen showed lymphosarcoma. External irradiation was administered. In January 1933 there was further evidence of recurrence in the cervical nodes, and the patient died in February.

*Comment.*—Case 1 is an example of generalized lymphosarcomatous disease in which the base of the tongue was one of the foci. The slow progress of the disease is noteworthy. Case 2 is an example of wide-

spread lymphosarcomatosis in which the tonsil was one of the numerous foci. Case 4 is another example of widespread disease in which a nasopharyngeal growth was present. The marked and rapid response to irradiation (figs. 2, 3 and 4) in the presence of widespread disease points to a bad ultimate prognosis. The rapid response to irradiation indicates a high degree of malignancy as well as marked radiosensitivity. In the other 3 cases the disease was more localized. Cases 3 and 5 illustrate the extension of the disease upward toward the accessory sinuses, with involvement of the cranial nerves. In case 3 the disease finally extended to the brain, causing paralysis of the facial nerve. In case 5 the disease extended upward, invaded the accessory nasal sinuses and ultimately caused total blindness. In spite of the wide local extent of the disease neither patient showed evidence of visceral metastases. In case 3 the absence of metastasis was proved at autopsy. The upward

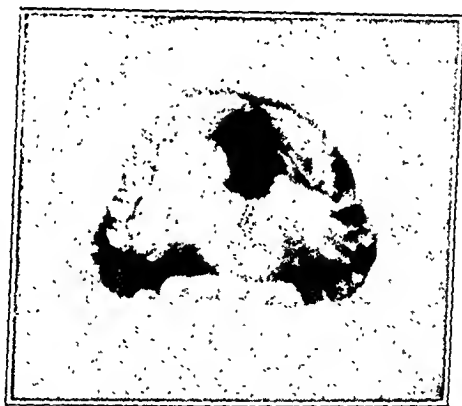


Fig. 5 (case 5).—A photograph showing perforation of the palate by a lymphosarcoma of the nasopharynx. The disease extended upward, causing total blindness.

extension of the disease is characteristic of lympho-epithelioma of the nasopharynx and accessory nasal sinuses. In these cases, evidence of involvement of the cranial nerves was also discovered with considerable frequency.

#### LYMPHOSARCOMA LIMITED TO THE RETROPERITONEAL LYMPH NODES

In some examples the lymphosarcomatous process is limited to the retroperitoneal lymph nodes. In these cases the presence of a retroperitoneal mass gives rise to a characteristic clinical entity. In other examples the retroperitoneal mass, while dominating the clinical picture, is associated with the disease in the other lymph nodes. Pressure on and involvement of the gastro-intestinal tract are not uncommon. In these cases the symptoms are essentially gastro-intestinal. The retroperitoneal

mass is highly radiosensitive, and startling primary regressions are usually noted after radiotherapy. However, the disease has a tendency to recur and to become widely disseminated. Following radiotherapy the patient may be clinically free from the disease for prolonged periods.

Minot and Isaacs<sup>5</sup> reported that 25 per cent of 477 patients with lymphoblastoma (exclusive of lymphatic leukemia) had as their initial symptom one referable to an abdominal lesion. Twenty per cent of a

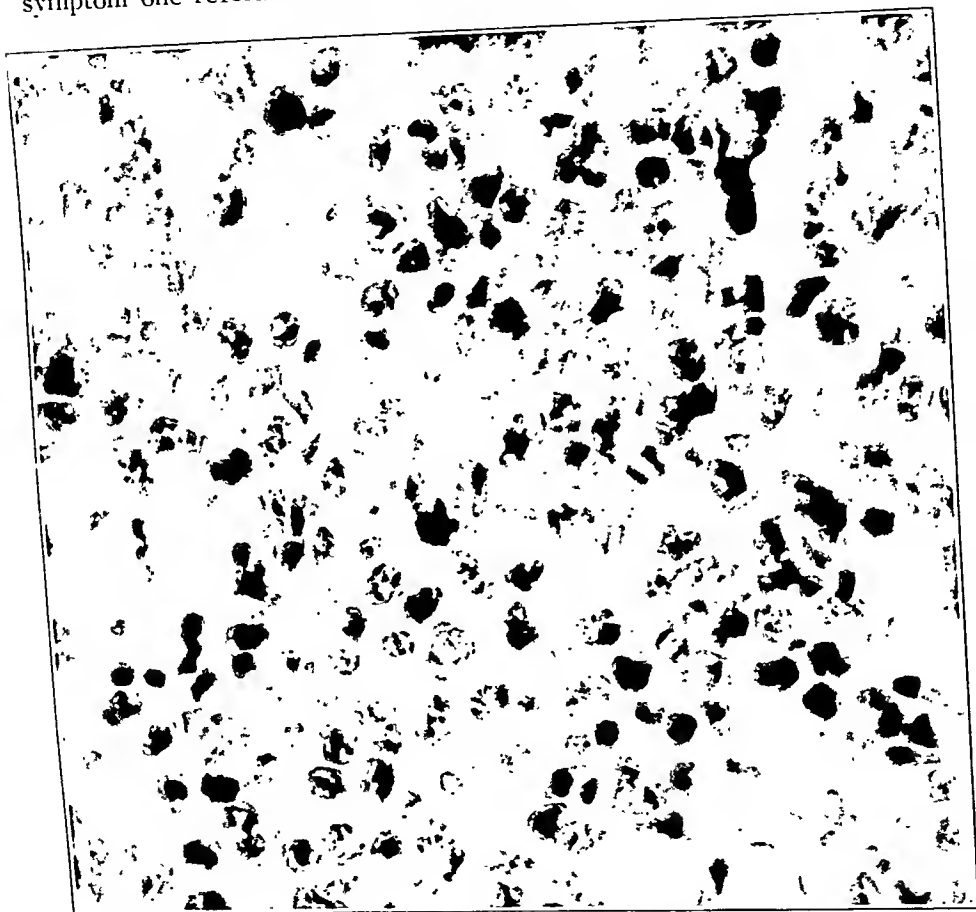


Fig. 6 (case 5).—A photomicrograph of a reticulum cell lymphosarcoma which began in the right nasopharynx and extended upward to the accessory nasal sinuses.

second group of 71 deceased patients without such initial symptoms had abdominal symptoms early in the course of their illness. Late in the disease abdominal symptoms occurred with great frequency. The pain, which was often intense, occurred in the abdomen and back or in the legs.

A résumé of the observations at autopsy (table 1) indicates that the retroperitoneal lymph nodes were involved in 8 of 13 cases. In this



series there was only 1 example in which the disease was localized in the retroperitoneal lymph nodes.

CASE 7.—J. M., a man aged 41, about August 1929 began to have vague abdominal distress accompanied by vomiting. Soon he suffered from fatigue on exertion, and there was gradual loss of weight. These symptoms continued for over two years before he was admitted to the hospital on Aug. 10, 1931. On examination a large, firm, fixed mass was discovered in the lower left quadrant of the abdomen. Evidence of nephritis and uremia soon developed, and the patient died. At autopsy it was found that the upper part of the left kidney and suprarenal gland were enveloped in a firm, white mass extending to and including the pancreas, which it bound firmly to the spine. The growth extended to the iliopsoas muscle and surrounded, but did not invade, the great vessels. The anatomic diagnosis was retroperitoneal lymphosarcoma invading one kidney and the pancreas. Histologically the tumor was a small cell lymphosarcoma.

#### LYMPHOSARCOMA ASSOCIATED WITH LESIONS OF THE RECTUM

Lymphosarcoma may affect any portion of the gastro-intestinal tract, including the appendix. The microscopic structure is that of either a small cell or a large round cell lymphosarcoma. In 1929 Bensaude, Cain and Horowitz<sup>6</sup> reported 3 cases, and after a thorough review of the literature stated that the subject had been so neglected that until 1929 they could find only 12 authentic cases in the literature. These authors distinguished two types: (1) a diffuse or generalized form, which is characterized by its structure, by its development and by its extension to the lymph nodes and (2) a localized form, which sometimes shows the typical structure of lymphosarcoma but most commonly resembles round cell sarcoma so closely that differentiation is extremely difficult. They reported 3 examples of the diffuse form.

One patient, aged 65, first had cervical, axillary and inguinal adenopathy which responded to radiotherapy. Five years later marked enlargement of one tonsil was noted; nine years after the onset of the disease a filling defect was demonstrated in the sigmoid flexure and on proctoscopic examination a nonulcerated mass was discovered, situated 12 cm. from the external anal orifice. Biopsy revealed a small cell lymphosarcoma. Roentgen therapy was administered, but the general condition of the patient became worse, and an ileostomy was performed because of obstruction. He died several months later of progressive cachexia.

The second patient was a woman, aged 74, in whom in 1924 there developed adenopathy in the left supraclavicular region. The nodes were removed one year later (1925), and a microscopic diagnosis of malignant lymphoma was made. In 1927 the patient was admitted with generalized adenopathy, abdominal masses and an enlarged spleen, all of which disappeared under radiation therapy. Rectal pain and constipation first appeared in October 1926. Rectal examination in March 1927 revealed a bulky, nonulcerated mass 4 cm. from the external anal orifice. A biopsy specimen showed lymphosarcoma. Radiotherapy resulted in the complete disappearance of the rectal growth, but the patient was lost sight of, and the ultimate result is not known.

6. Bensaude, R.; Cain, A., and Horowitz: *Le lymphosarcome du rectum*, Ann. de méd. 26:405 (Dec.) 1929.

The third patient was a woman, aged 67, in whom, in December 1928, there first developed bilateral cervical and preauricular adenopathy followed by severe intractable diarrhea. Examination revealed extensive adenopathy on the left cervical and supraclavicular side. Proctoscopic examination revealed a large, nonulcerated mass about 12 cm. high, which on microscopic examination proved to be a reticulum cell lymphosarcoma. The patient died. Autopsy revealed involvement of the peribronchial, retroperitoneal and mesenteric nodes. The rectum showed diffuse involvement in the lymphosarcomatous process.

Bensaude, Cain and Horowitz<sup>6</sup> cited 9 cases (reported by other authors) of localized lymphosarcoma of the rectum. Noel Lapeyre's<sup>7</sup> patient was a woman, aged 28, in whom there developed a bulky tumor above the sphincter of the rectum. Rectal amputation was performed. Microscopically there were hypertrophied lymph follicles which could be traced to the fully developed neoplastic process. The patient reported on by Stolz, Gunsett and Oberling,<sup>8</sup> aged 66, had an ulcerated tumor which extended 5 cm. along the lower portion of the rectum without causing stenosis and was fixed to the sacrum posteriorly and to the vagina anteriorly. The tumor was regarded as inoperable. The treatment consisted of radium puncture by the vaginal and by the rectal routes supplemented by external irradiation. The tumor disappeared, and the patient had remained well for over six years when the report was made. Hessert's<sup>9</sup> patient was 50 years of age. The growth was resected, and the patient was free from disease seven months later. In his original contribution Kundrat<sup>1</sup> mentioned 1 case of inoperable tumor of the rectum which was diagnosed clinically as cancer, but which at autopsy proved to be lymphosarcoma. Key's<sup>10</sup> patient was 41 years of age. A slowly growing, nonulcerated tumor of the rectum developed just above the sphincter. Partial removal of the mass was followed one month later by recurrence and extension of the disease. Exner's<sup>11</sup> patient, a man, aged 43, suffered from a circumscribed, ulcerated tumor of the midportion of the rectum. The rectum was removed, and microscopic examination of the growth revealed a small round cell lymphosarcoma. The patient was well two years later. A second patient of Exner presented a mushroom-like tumor which on resection proved to be a lym-

7. Lapeyre, N. C.: Primary Sarcoma of Rectum, *Rev. de chir., Paris* **58**:223 and 281, 1920.

8. Stolz, J.; Gunsett, A., and Oberling, C.: Lymphosarcome du rectum. Radio et Curiothérapie. Guérison depuis six ans, *Bull. Assoc. franç. p. l'étude du cancer* **17**:63 (Feb.) 1928.

9. Hessert, W.: Lymphosarcoma of Rectum; *Ann. Surg.* **36**:459 (July-Dec.) 1902.

10. Key, E.: Drei Fälle von Rektalsarkom, *Nord. med. Ark.* **51**:26, 1905; *Zur Kasuistik des Rektalsarkoms.* *ibid.* **8**:1, 1908.

11. Exner, A.: Ueber nichtmelanotische Sarkome des Mastdarms, *Med. Klin.* **4**:858, 1908.

phosarcoma. Brachmann's patient was 15 years of age. A rectal tumor the size of a cherry proved on section to be a small round cell sarcoma, probably lymphosarcoma.

CASE 8.—F. S., a man aged 41, had suffered from diarrhea and rectal discomfort for two years. On rectal and proctoscopic examination a nodular growth 3 cm. in diameter was discovered on the anterior wall of the rectum 4 cm. above the anal sphincter. The tumor was not ulcerated and was firmly attached to the underlying structures. A wide surgical excision of the growth was performed, followed by irradiation with high voltage roentgen rays. Microscopic examination of the specimen revealed lymphosarcoma. The operation was performed in June 1931. The patient is free from the disease at the time of writing, three years later.

CASE 9.—H. H., aged 48, complained of pain in the lower portion of the abdomen of six months' duration but had no other symptoms. On examination there was a growth the size of a lime just above the anal sphincter. A biopsy proved it to be lymphosarcoma. The treatment consisted of the implantation of removable platinum radium needles and external radiation with the 4 Gm. radium "bomb." The tumor disappeared promptly, and the patient has been free from the disease for fourteen months at the time of writing. At no time was there evidence of the disease in other parts of the body.

CASE 10.—H. F., 53 years of age, for six months had had symptoms consisting of intermittent diarrhea alternating with constipation and some bleeding. No pain had been experienced, and there had been no loss of weight. Examination revealed a lymphosarcoma at the rectosigmoid junction. Radium therapy resulted in the complete disappearance of the growth. Six months later there developed generalized adenopathy with enlargement of the submaxillary, cervical, axillary and inguinal nodes. The lesions responded to external therapy with the radium bomb, and the patient is now clinically free from the disease at the time of writing, one year and a half after the onset of symptoms and thirteen months after beginning the treatment.

*Comment.*—In case 8 a patient with localized lymphosarcoma was free from the disease three years after wide surgical removal of the lesion followed by irradiation. The most common site of the lesion is just above the sphincter, although the growth may appear at the rectosigmoid junction or anywhere along the colon or ileum. The perirectal and pelvic tissues are rarely invaded. The lesion usually covers a large area, presenting an irregular surface of the mucous membrane, which is frequently not ulcerated. The nodules are firm and elastic, lacking the induration of cancer. The localized forms frequently occur as more or less bulky masses just above the anal sphincter and are sometimes attached to a pedicle.

Persistent diarrhea which refuses to submit to medication is the most important clinical sign. Frequently there are alternating constipation and diarrhea. The course of the disease varies markedly, depending chiefly on whether the lesion is isolated and localized, or is part of generalized lymphosarcomatosis.

Cure of localized lymphosarcoma of the rectum is recorded by wide surgical extirpation alone, by adequate radiotherapy alone and by the

combined methods. In general, because of the marked radiosensitivity of the lesions, radiotherapy constitutes the method of choice. In certain cases treatment by interstitial radiation is useful. External irradiation should be utilized in all cases either alone or in conjunction with radium puncture or surgical excision, depending on the size, location and radiosensitivity of the tumor.

#### LYMPHADENOMA (LYMPHOMA)

Chronic enlargement of the lymph nodes limited to a group of nodes and not becoming generalized have been described by LeCount<sup>12</sup> as being of common occurrence. Under the terms "simple lymphoma," "lymphadenoma" and "hyperplastic lymphadenitis," Ewing<sup>2</sup> has given the following description of the pathologic observations:

Appearing in the neck, axilla, groin and subcutaneous tissues and sometimes in other regions, these groups of enlarged nodes form solid tumor-like masses, with little or no tendency to central necrosis. After reaching a certain size they may remain stationary for months or years, producing only local symptoms. The prolonged benign course is characteristic (LeCount's case continued for fifteen years). The structure is characterized by diffuse overgrowth of typical small lymphocytes. The lymph follicles in the early stages are increased in size and in number and exhibit prominent germ centers. The pulp tissue is composed of closely packed lymphocytes. The structure resembles that found in leukemia and pseudoleukemia. It may be distinguished from the former by the blood test and from the latter by its local character. The differentiation from lymphosarcoma may be difficult. The distinction must be made by the usual clinical and microscopic criteria of malignancy. One case, observed by Ewing, persisted for eighteen years, eventually proving fatal, with rapid local growth and asphyxia.

CASE 11.—M. E., a man aged 61, first noted enlargement of the submental nodes three months before his first admission to the hospital on Feb. 6, 1931. Soon afterward he noticed enlargement of the cervical and inguinal nodes and pain in both legs. Examination revealed enlarged discrete nodes in the cervical, axillary and inguinal regions. Roentgen examination of the chest revealed a homogeneous shadow at the base of the left lung, a sharply defined shadow in the region of the great vessels and an increased density at the right hilus. Roentgen therapy was administered over the cervical, axillary and inguinal regions and over the lungs and mediastinum with pronounced and rapid response. Ten months later the patient was treated for enlargement of the submental and supraclavicular nodes. Twenty months after the second recurrence he was readmitted with dyspnea, cough, expectoration, edema of the extremities and pain in the back. Examination revealed generalized adenopathy, ascites and myocardial disease. Irradiation again resulted in marked regression of the nodes and improvement in

12. LeCount, E. R.: Lymphoma: A Benign Tumor Representing a Lymph Gland in Structure. *J. Exper. Med.* 4:559, 1899.

the patient's general condition. The microscopic examination of a lymph node removed for biopsy revealed a structure characteristic of lymphadenoma (fig. 7). The patient is alive at the time of writing, three and one-half years after the onset of symptoms. The roentgen observations on the mediastinum taken three years apart are of interest (fig. 8).

CASE 12.—R. V., a white man aged 43, first noted a mass in the left inguinal region in March 1928. In February 1931 a small tumor was removed from the

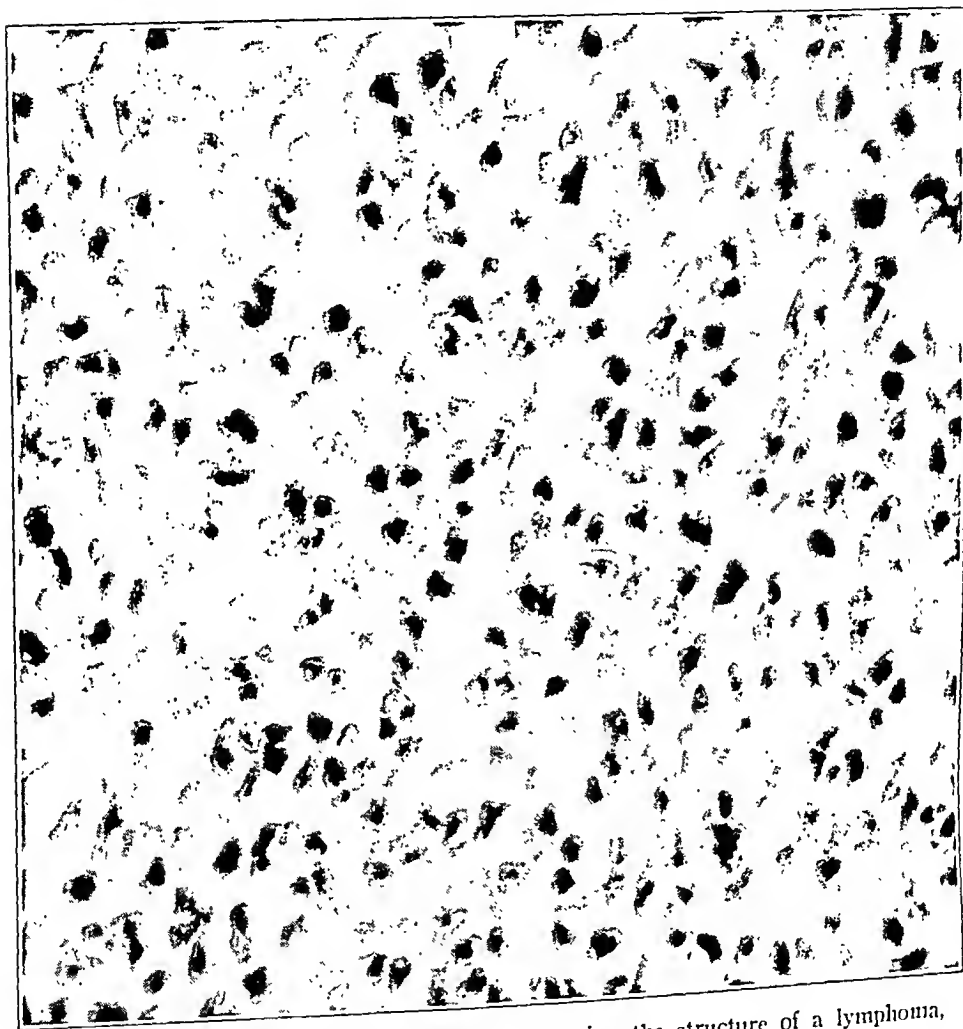


Fig. 7 (case 11).—A photomicrograph showing the structure of a lymphoma, or lymphadenoma, with the complete loss of the architecture but absence of the characteristics of fully developed lymphosarcoma.

left groin. Three weeks later he was admitted to the hospital for postoperative irradiation. Microscopic examination of tissue removed at the operation revealed the characteristic features of lymphoma. There was a partial loss of the architecture, with the lymph follicles still recognizable. In the center of some of the follicles occasional mitotic figures were seen (fig. 9). External radiation was given over the operative site. In December 1932 enlarged nodes appeared in the right inguinal region and disappeared after external irradiation with roentgen rays. At



Fig. 8 (case 11).—Roentgenograms of the lungs. *A* shows a widening of the lower part of the mediastinum before treatment. The microscopic diagnosis was lymphadenoma. *B* shows the same area three years later at the time of a local recurrence of the disease.

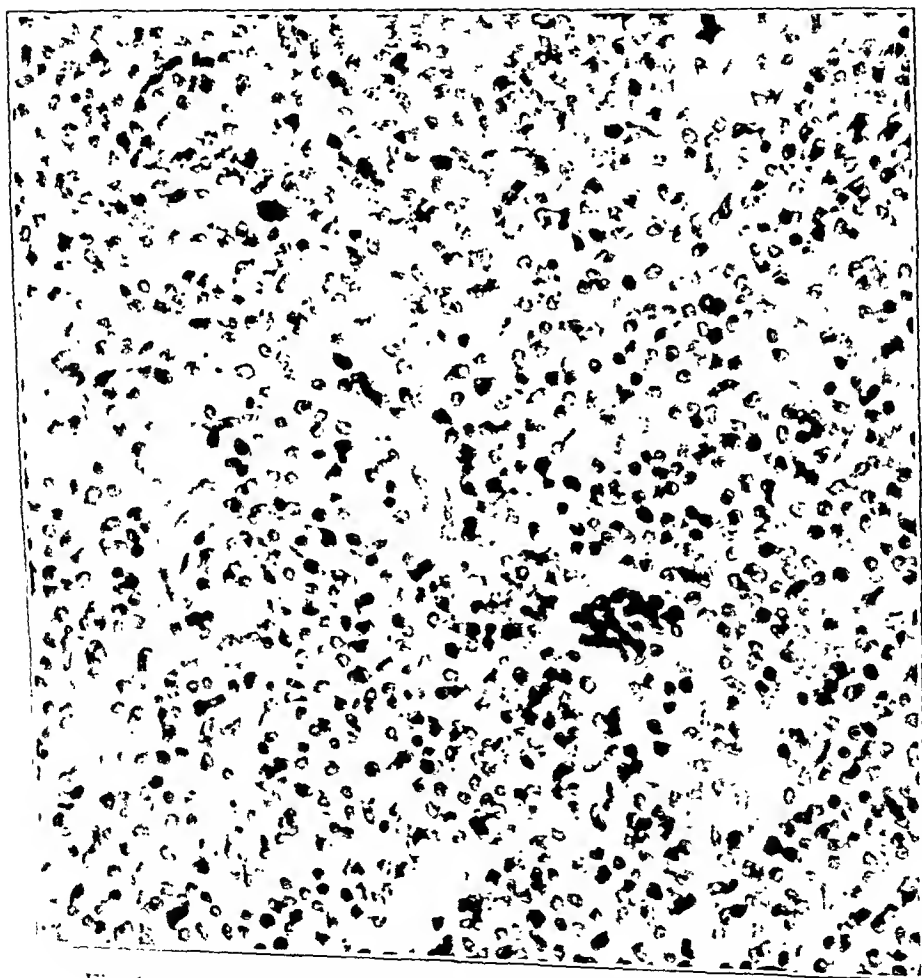


Fig. 9 (case 12).—A photomicrograph showing the structure of a lymphoma, or lymphadenoma. There is a partial loss of the architecture, but the cells are typical, with only occasional mitoses. The structure lacks the characteristics of fully developed lymphosarcoma.

the present writing the patient is alive but shows evidence of recurrence in the left inguinal region, with edema of the left leg. He is under treatment.

CASE 13.—J. G., a man aged 56, first noted a small swelling in the right side of the neck about 1930. It increased in size until it involved both sides of the neck. Soon afterward there developed dyspnea, fatigue on exertion, palpitation, vertigo and dysphagia. Examination revealed marked bilateral enlargement of the cervical, axillary and inguinal lymph nodes. The microscopic examination of a node removed for biopsy revealed a structure characteristic of lymphadenoma. In May 1933 external radiation was administered to all the lymph node areas with marked improvement. In December 1933 the patient was readmitted to the hospital on account of recurrence, and irradiation again resulted in a marked regression of the lesions. As in the preceding cases the adenopathic processes exhibited a high degree of radiosensitivity.

#### THYMIC TUMORS

The classification of thymic neoplasms has presented formidable difficulties, mainly because of the lack of knowledge concerning the

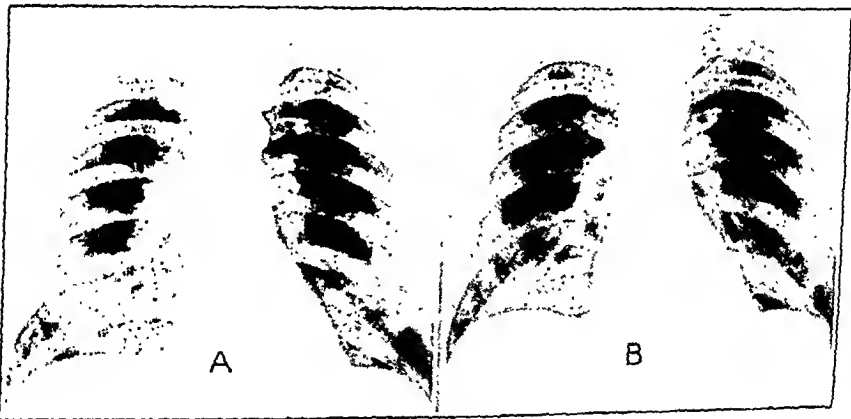


Fig. 10 (case 14).—Roentgenograms of the lungs. *A* shows a widened mediastinal shadow before roentgen therapy. The microscopic diagnosis was thymoma. *B* shows the same area eight months after treatment.

histogenesis of the thymic cells or the so-called thymic lymphocytes forming the reticulum and parenchyma of the thymus gland. This difficulty is intensified by the extreme variations in the histologic structure of these tumors, which render a histologic classification highly confusing and extremely uncertain.

According to Ewing<sup>2</sup> thymic tumors fall into two main groups: (1) lymphosarcoma or thymoma, composed of round, polyhedral and giant cells, and (2) carcinoma, arising from the reticulum cells. Lymphosarcoma is the more common of the two, and Ewing found little difficulty in distinguishing thymic tumors at autopsy from tumors of the mediastinal lymph nodes or the lungs. Thymic tumors have a tendency to surround and compress the trachea, bronchi, pericardium and great vessels. The bronchial, cervical and axillary nodes are frequently

involved. Extension and metastases to the following organs are of common occurrence: pleura, lungs, pericardium, spleen, liver, suprarenal glands, pancreas, kidneys and brain. Perforation of the sternum is not uncommon, and cases of metastases to bones have been recorded.

Histologically, some forms of thymoma resemble Hodgkin's disease, while others possess the characteristic features of lymphosarcoma. The thymic carcinomas are composed of pavement, cuboidal or cylindric epithelium. Mixed forms have been recorded by various observers.

Margolis<sup>13</sup> reviewed the literature on the histogenesis, pathology and the classification of thymic tumors and presented an excellent critical review of the subject. Two opposite views are held as to the histogenesis of the thymic cells. Some authors have held that the small thymic cells are related to the blood lymphocytes and that they are therefore of mesenchymal origin (Maximow,<sup>14</sup> Blum, Pinner<sup>15</sup> and Hammar<sup>16</sup>). Another group of workers advance the belief that the small thymic cells arise from the entodermal thymic reticulum (Nusbaum and Prymak,<sup>17</sup> Stöhr,<sup>18</sup> Bell,<sup>19</sup> Prenant, Dustin<sup>20</sup>). Margolis reported 6 cases of thymic tumor and arrived at the following conclusions:

A rigid classification of tumors of the parenchyma is not possible at present because of the lack of definite knowledge concerning the histogenesis of all the elements of the thymic parenchyma, and because of the marked polymorphism of the cells which constitute most of such tumors. For this reason the designation

---

13. Margolis, H. M.: Tumors of Thymus: Pathology, Classification and Report of Cases, *Am. J. Cancer* (supp.) **15**:2106 (July) 1931.

14. Maximow, A.: Untersuchungen über Blut und Bindegewebe: II. Ueber die Histogenese der Thymus bei Säugetieren, *Arch. f. mikr. Anat.* **74**:525, 1909; IV. Ueber die Histogenese der Thymus bei Amphibien, *ibid.* **79**:569, 1912; V. Ueber die embryonale Entwicklung der Thymus bei Selachiern, *ibid.* **80**:39, 1912; A Textbook of Histology, completed and edited by W. Bloom, Philadelphia, W. B. Saunders Company, 1930.

15. Pinner, Max: Zur Frage der kleinen Thymusrindenzellen, Frankfurt. *Ztschr. f. Path.* **23**:479, 1920.

16. Hammar, J. A.: Zur Kenntnis der Teleostierthymus, *Arch. f. mikr. Anat.* **73**:1, 1908; Ueber Thymusgewicht und Thymuspersistenz beim Menschen, *Anat. Anz.* (supp.) **27**:121, 1905.

17. Nusbaum, J., and Prymak, T.: Zur Entwicklungsgeschichte der lymphoiden Elemente der Thymus bei den Knochenfischen, *Anat. Anz.* **19**:6, 1901.

18. Stöhr, P.: Ueber die Natur der Thymus-Elemente, *Anat. Hefte* **31**:407, 1906.

19. Bell, E. T.: Tumors of the Thymus, *J. Nerv. & Ment. Dis.* **45**:130 (Feb.) 1917.

20. Dustin, A. P.: Recherches d'histologie normale et expérimentale sur le thymus des amphibiens anoures, *Arch. de biol.*, Paris **28**:1, 1913; A propos d'une thèse récente sur la biologie du thymus, *Arch. de zool., expér. et gén.* **55**:95, 1915-1916.





Fig. 11 (case 14).—*A*, a low power photomicrograph, shows a carcinoma of the thymus. *B* is a high power photomicrograph of the same section. The lesion proved to be moderately radiosensitive.

of thymoma for all tumors derived from the parenchyma of the organ seems more satisfactory than their classification as carcinomas and lymphosarcomas. Careful study of tumors of the thymus of the type often designated lymphosarcoma suggests that the sarcomatous appearance of the tissue may represent only a morphologic variation of a type of cell derived from the thymic reticulum. For the present the designation of sarcoma, including lymphosarcoma of the thymus, should be reserved for those tumors apparently derived from elements within the stroma of the thymus.

Crosby<sup>21</sup> collected 166 cases of malignant disease of the thymus gland. In 122 of these the growth was classified as sarcoma and in 44, as carcinoma. In a series of cases of mediastinal neoplasms Haagensen<sup>22</sup> reported 2 cases of carcinoma of the thymus with complete clinical and pathologic data, including observations at autopsy. He emphasized their radioresistance and called attention to the importance of this fact

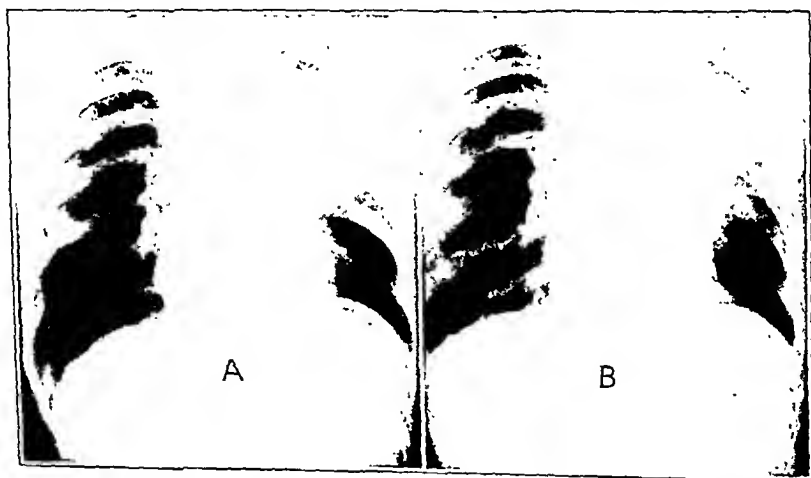


Fig. 12 (case 15).—Roentgenograms of the lungs. *A* shows an extensive mediastinal mass, probably originating in the thymus, before treatment; *B* shows the same area after treatment. The lesion proved to be radioresistant.

in relation to the differential diagnosis of primary mediastinal tumors. In 1932 Craver and MacComb<sup>23</sup> reported 3 cases of tumefaction of the thymus in association with lymphatic leukemia and reviewed the literature. The high radiosensitivity of the lesion was noted, and attention was directed to the importance of a careful investigation of the blood and of the lymph nodes when enlargement of the thymus is discovered.

21. Crosby, E. H.: Malignant Tumors of Thymus Gland, *Am. J. Cancer* **16**: 461 (May) 1932.

22. Haagensen, C. D.: Differential Diagnosis of Primary Neoplasms of Mediastinum, *Am. J. Cancer* **16**:723 (July) 1932.

23. Craver, L. F., and MacComb, W. S.: Lymphatic Leukemia with Thymic Enlargement, *Am. J. Cancer* **16**:277 (March) 1932.

CASE 14.—W. C., a man aged 44, noted a painless swelling on the right side of the neck in May 1927. In January 1928 a biopsy on the cervical mass was reported to show lymphosarcoma. External radiation resulted in the complete disappearance of the mass. The patient remained well for five years, when a local recurrence was noted in the same area. Examination in March 1933 revealed a mass 15 by 6 cm. reaching from the right mastoid process to the angle of the jaw. There was no other adenopathy. Roentgen examination of the lungs revealed a mediastinal shadow (fig. 10 *A*). External irradiation with roentgen rays resulted

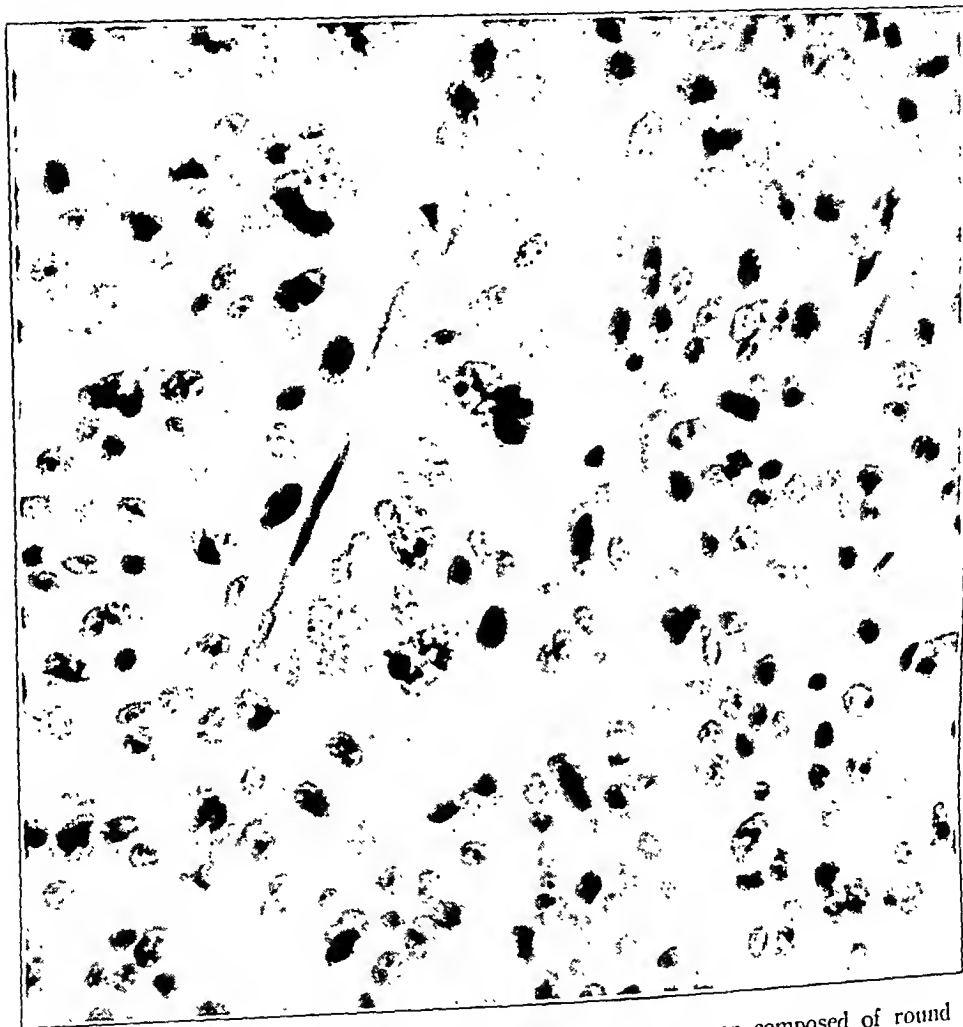


Fig. 13 (case 15).—A photomicrograph showing a tumor composed of round and polyhedral cells with numerous giant cells, probably of thymic origin.

in the rapid regression and disappearance of both the cervical and the mediastinal mass (fig. 10 *B*). The patient is clinically free from the disease at the time of writing, more than six years after the onset and one year after the last treatment. A review of the microscopic sections prepared in 1928 shows that the structure is composed essentially of cylindric cells in a plexiform arrangement. The nuclei are large and clear, with no nucleoli. In certain areas there are giant cells which resemble Hassall's corpuscles. The structure is consistent with a diagnosis of a tumor of thymic origin (fig. 11).

The unusual features of this case were: (1) that the patient was alive and clinically free from the disease nearly seven years after the onset; (2) the long interval of five years between the first treatment of the cervical adenopathy and the local recurrence, and (3) the radiosensitivity of the tumor at the time of the



Fig. 14 (case 16).—*A* shows the invasion of the soft parts over the anterior wall of the chest by tumors from a primary thymic tumor. *B* shows the same area three weeks after treatment.

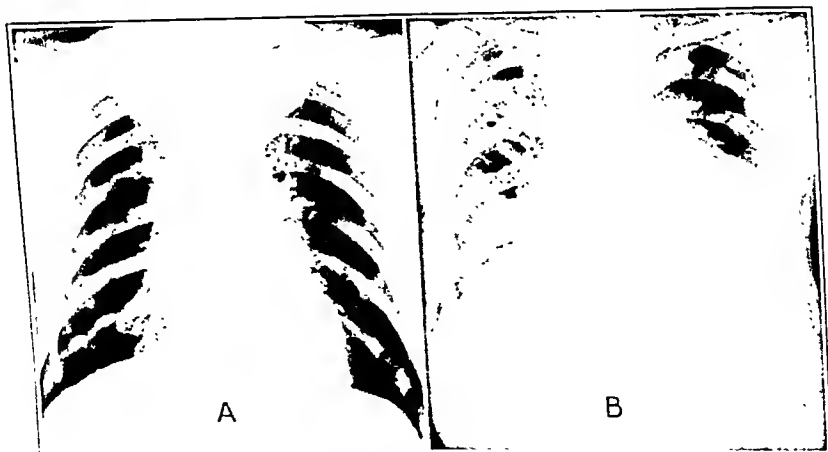


Fig. 15 (case 16).—Roentgenograms of the lungs. *A* shows a primary mediastinal thymoma; *B* shows an extension of the disease in the mediastinum six weeks later.

second irradiation. It is of special interest that the result was so good in spite of the high degree of radiosensitivity of the tumor. Usually those tumors which respond rapidly are so highly malignant that they are accompanied by a grave prognosis.

CASE 15.—G. H., a man aged 39, had pain in the chest and in the back in August 1930. These symptoms were soon followed by dyspnea, cough, swelling of the neck, hoarseness and loss of weight. Examination revealed engorgement of the veins of the neck and physical signs of a mediastinal mass. Roentgen examination of the chest revealed a large mediastinal mass extending from the hilus of the left lung at the level of the third rib outward toward the periphery (fig. 12). The trachea was displaced markedly to the right. There were discrete enlarged nodes in both cervical areas and in the right axillary and right inguinal regions. High voltage roentgen therapy was instituted, but the patient's general condition grew worse, and he died two weeks after therapy was begun. Autopsy revealed a mediastinal tumor with extension to the pleura and the pericardium, metastases to the peritoneum, the liver and the pancreas and gangrene of the left lung.



Fig. 16 (case 16).—A photograph of the gross specimen of a mediastinal tumor removed at autopsy. It appears to have originated in the thymus.

Examination of the microscopic sections revealed diffuse small round cell lymphosarcoma with occasional giant cells resembling Hassall's corpuscles (fig. 13). The failure of the lesion to respond to irradiation is probably best explained by the extent of the disease and by the poor general condition of the patient rather than by an inherent radioresistance of this particular type of tumor.

CASE 16.—C. B., a man aged 44, was admitted to the hospital on Aug. 27, 1933, with a history that five months previously he noted nodular masses in the skin over the anterior wall of the chest. These were followed by the appearance of similar lesions in both axillae. Examination revealed multiple nodular tumors over the sternum and in both axillae and groins (fig. 14). Roentgen examination on August 28 disclosed a well defined tumor in the mediastinum, and a roentgenogram taken on October 13 showed marked advancement of the process (fig. 15).

Microscopic examination revealed a sarcoma composed of round and polyhedral cells, suggestive of thymic origin. Radium pack therapy was administered daily from September 9 to September 24, alternately to the upper and the lower portions of the sternum (at a distance of 15 cm., with a portal of 10 cm. and with a dosage of 50,000 mg. hours). This resulted in the disappearance of all the tumors. In spite of the local regression the patient soon became jaundiced. His general condition grew progressively worse, and he died thirty-seven days after treatment was begun.

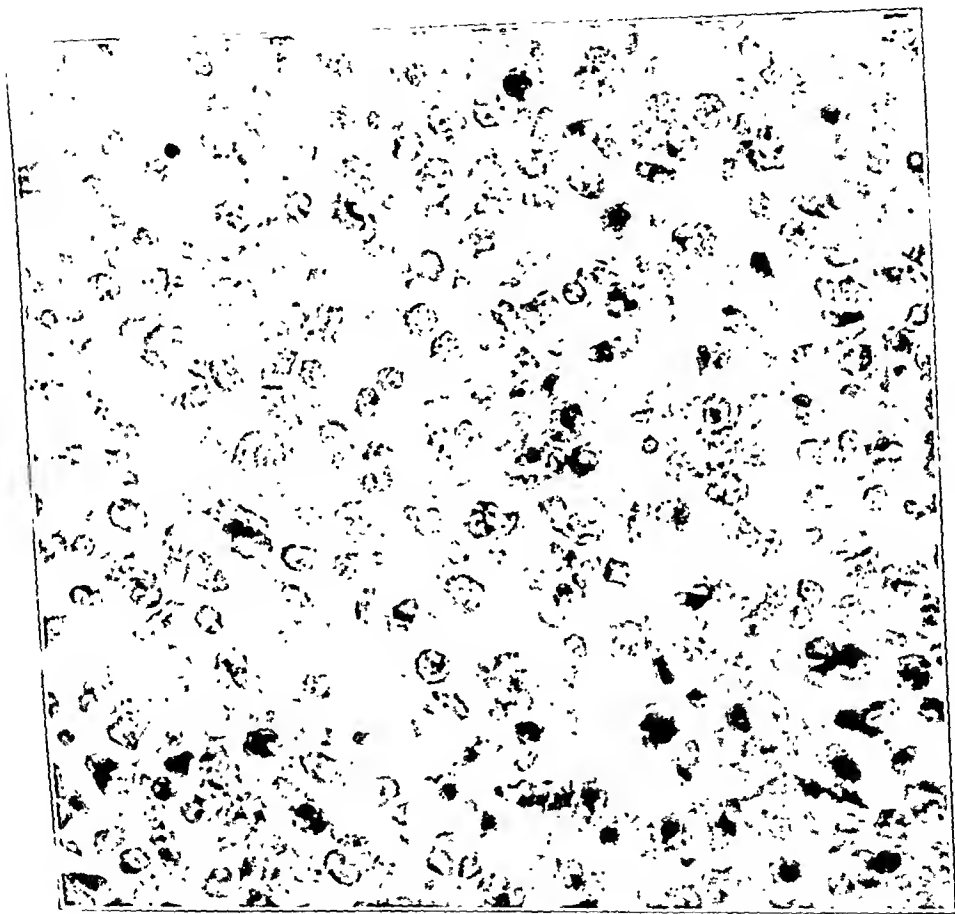


Fig. 17 (case 16).—A photomicrograph showing the structure of the thymic tumor depicted in figure 16, which was that of reticulum cell lymphosarcoma. The tumor proved to be highly radiosensitive, but treatment was followed by prompt recurrence, extension of the disease and death.

Autopsy revealed a severe degree of jaundice, cutaneous and subcutaneous tumor nodules and invasion of the lymph glands in the neck, axillae, groins, mediastinum and retroperitoneal areas. In the region of the thymus there was a discrete tumor which had the anatomic position of the thymus (fig. 16). Examination of the microscopic sections revealed a malignant tumor composed of round and polyhedral cells, growing diffusely, with numerous mitoses (fig. 17).

This case is an example of a rapid primary response to irradiation followed by prompt recurrence in a patient in whom the disease was widespread throughout the body.

CASE 17.—J. H., a man aged 43, was admitted to the hospital on March 8, 1933, with a history that in February 1932 he had dyspnea, weakness and pain in the chest, followed by cough, abdominal pain and the loss of 60 pounds (27.2 Kg.) over a period of six months. Three weeks before admission swelling of the sternum was noted, and one week before admission large masses appeared in both sides of the neck and in the right axilla. Examination revealed marked emaciation and a large, pyramid-shaped swelling of the upper two thirds of the sternum. There were enlarged, discrete nodes in both cervical and axillary regions. Roentgen examination of the chest revealed a large mediastinal mass extending widely in all directions (fig. 18 *A*). A lymph node was excised from the right axilla, which on microscopic examination revealed the typical structure of reticulum cell lymphosarcoma (fig. 19). Roentgen therapy resulted in prompt regres-

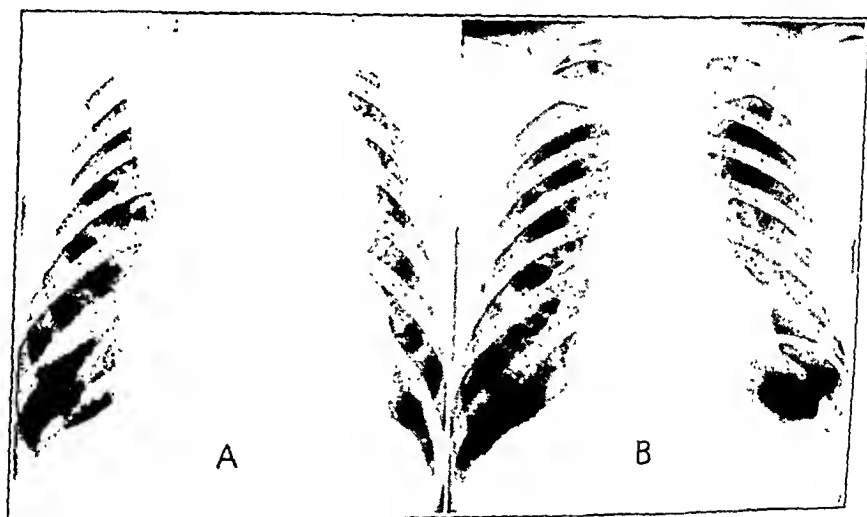


Fig. 18 (case 17).—Roentgenograms of the lungs. *A* shows a huge mediastinal mass before treatment; *B* shows the same area three months later, with almost complete disappearance of the lesion after roentgen therapy. This is an example of a highly radiosensitive lesion.

sion of the sternal tumor and mediastinal mass, as noted by repeated roentgen examination of the chest. The general condition of the patient improved, and his symptoms disappeared. Two months after treatment was begun there was a marked reduction in the size of the mediastinal mass, and three months after the beginning of treatment a roentgen examination of the chest revealed no demonstrable evidence of disease in the mediastinum (fig. 18 *B*). The patient was last seen in March 1934. His general condition was good, he had no disturbing symptoms, and a roentgenogram of the chest revealed a normal mediastinum (fig. 20).

The mass in this case is an example of a highly radiosensitive tumor which responded to roentgen therapy. It is of interest that whereas the mediastinal mass proved to be radiosensitive, it was not extremely so, as indicated by the fact that the roentgenogram of the chest made two months after

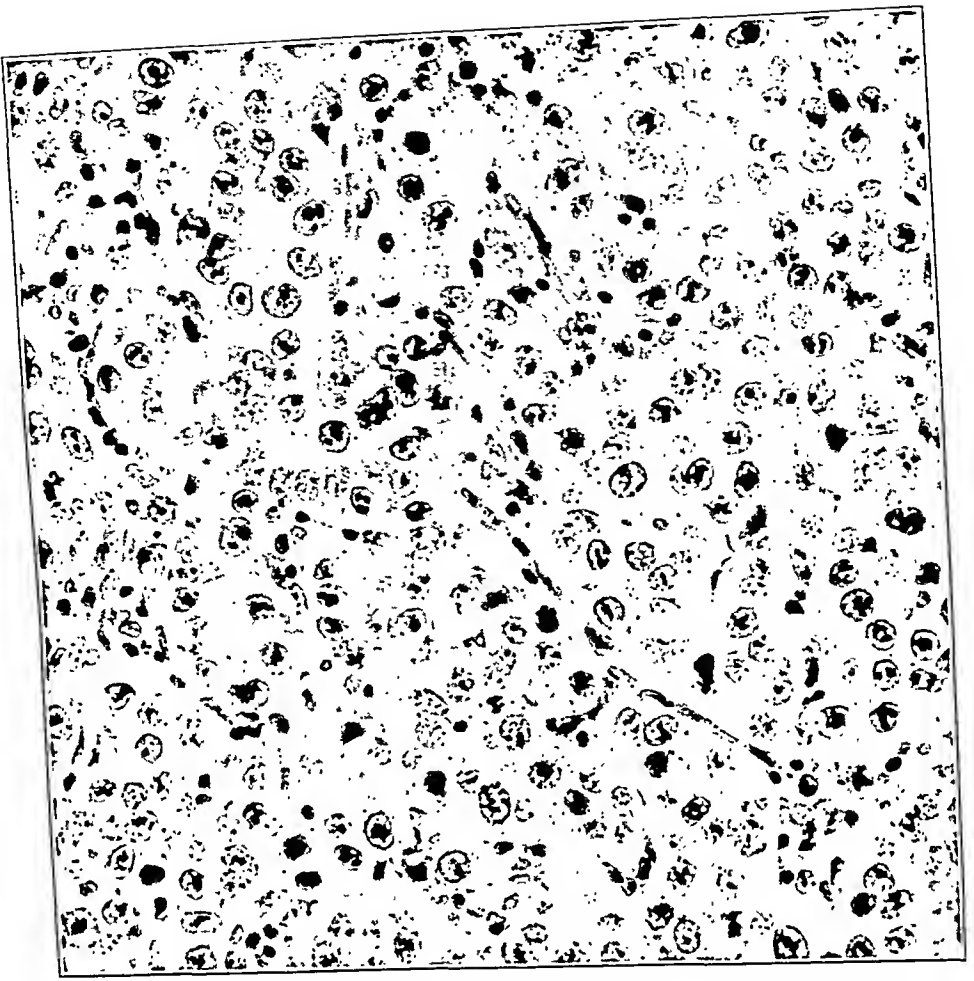


Fig. 19 (case 17).—A photomicrograph showing the structure of a reticulum cell lymphosarcoma, probably of thymic origin.



Fig. 20 (case 17).—A roentgenogram showing the appearance of the lungs fourteen months after treatment.



treatment failed to show complete regression. This is an example, therefore, of the better prognosis in cases of tumor which, although sensitive to radiation, do not regress too rapidly.

CASE 18.—W. C., a man aged 37, was admitted to the hospital on Aug. 21, 1930, with a history that six weeks previously he had begun to suffer from vague pains throughout the skeletal system, enlarged cervical glands, weakness and loss of weight. Examination revealed that the patient was markedly undernourished. The cervical and supraclavicular glands were enlarged, and roentgen examination of the chest revealed a widened mediastinal shadow (fig. 21). Microscopic examination of a lymph node revealed a structure resembling that of thymic carcinoma. The lesion failed to respond to irradiation. The patient's general condition became rapidly worse, and he died fifty days after admission.

The growth in this case is an example of the radioresistant form of thymic tumor. The microscopic structure was consistent with the failure of the growth to respond to treatment.

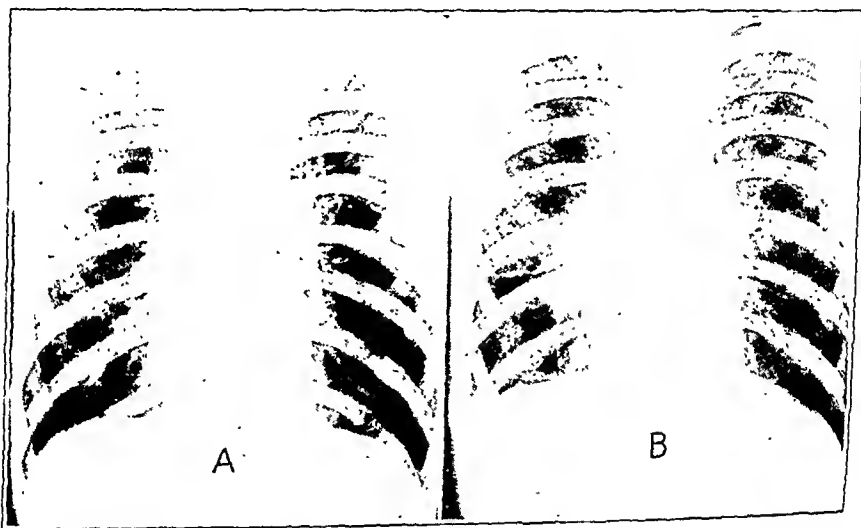


Fig. 21 (case 18).—Roentgenograms of the lungs. *A* shows a mediastinal mass, probably of thymic origin, before treatment; *B* shows the same area after treatment.

CASE 19.—W. P., a white man aged 34, was admitted to the hospital on June 2, 1932. Symptoms were present for fourteen months and consisted of pain, dysphagia, dyspnea, cough and attacks of fainting. The examination disclosed dilatation of the veins of the neck and chest, pleural effusion at the base of the right lung and enlarged axillary nodes. A biopsy specimen revealed a tumor composed of round and polyhedral cells with numerous giant cells (fig. 22). Roentgenograms of the chest revealed a marked accentuation of the mediastinal shadow on both sides and a pleural effusion on the right side (fig. 23). The tumor regressed rapidly, and on August 24 the mediastinum appeared to be normal. Three months later the disease recurred and the patient died. Autopsy revealed a tumor involving the axillary, mediastinal, retroperitoneal and mesenteric lymph nodes, with extension to the pleura and pericardium and metastases to the liver and spleen.

CASE 20.—L. O., a white man aged 54, was admitted to the hospital on Sept. 13, 1932. His general health was good until three months prior to admission, at which time he began to have enlarged cervical glands, pain in the left side of the chest, dyspnea and cough and considerable loss of weight. The physical examination disclosed a marked bulging of the anterior wall of the chest on the left in the region of the border of the sternum. There were also an enlarged, firm, movable lymph node in the left supraclavicular region and enlarged glands in the left

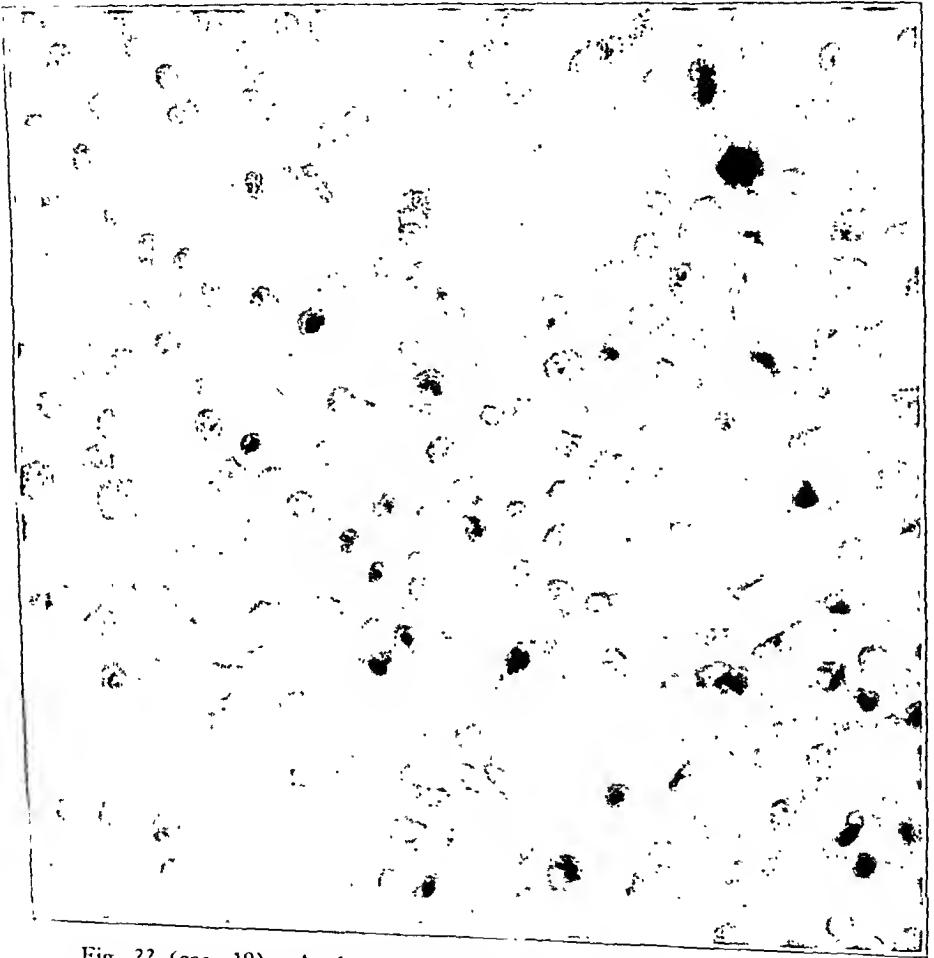


Fig. 22 (case 19).—A photomicrograph of a section of a tumor composed of round and polyhedral cells, with many giant cells present. The tumor was probably of thymic origin. The lesion responded rapidly to irradiation but recurred promptly.

axilla. The veins in the neck were markedly distended. Microscopic examination of tissue from the sternum revealed a structure typical of thymoma. Roentgenograms revealed an extensive mediastinal mass located chiefly on the left side. There was also considerable fluid in the left pleural cavity. One thousand cubic centimeters of dark, amber-colored fluid was withdrawn by paracentesis from the

left pleural sac. Roentgen treatment was instituted on September 30. There was slight clinical improvement, but the disease recurred promptly, and the patient died outside the hospital in January 1933, about three months after the first roentgen treatment.

CASE 21.—C. R., a white man aged 56, was admitted to the hospital on April 20, 1932. According to the history his neck began to swell two months prior to admission and rapidly increased in size, accompanied by cough and dyspnea. Examination revealed marked cervical adenopathy. Microscopic examination of the biopsy specimen revealed a thymic carcinoma (fig. 24). Roentgen examination of the chest revealed an abnormal shadow of heavy density superimposed on the upper portion of the mediastinum (fig. 25 *A*). The patient received two courses of high voltage roentgen therapy in April and May and in August and September. There was only moderate response to irradiation as shown by a slight diminution



Fig. 23 (case 19).—A roentgenogram showing a tumor in the mediastinum and fluid at the base of the right lung.

of the mediastinal shadow (fig. 25 *B*). The patient committed suicide on October 4, after he was discharged from the hospital.

#### PRINCIPLES AND TECHNIC OF TREATMENT

It is evident from the gross anatomy of lymphosarcoma that comparatively large masses of tumor tissue must be exposed to radiation and that because of its widespread distribution extensive areas of the body must be treated. Were it not for the high degree of radiosensitivity of the tumor, the doses required to control the disease would be far greater than the general condition of the patient would tolerate. However, the degree of radiosensitivity is so high that relatively small

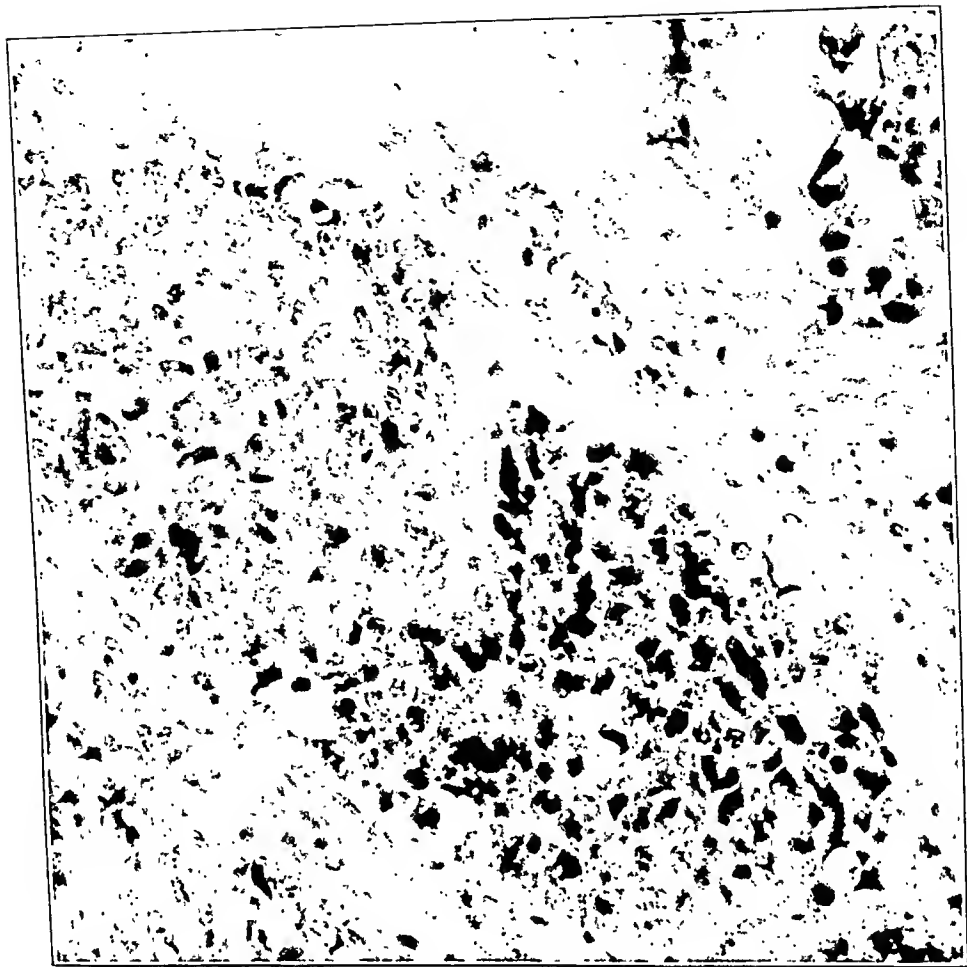


Fig. 24 (case 21).—A photomicrograph showing carcinoma of the thymus. The lesion proved to be radioresistant.



Fig. 25 (case 21).—Roentgenograms of the lungs. *A* shows a tumor in the mediastinum before treatment. The microscopic diagnosis was thymic carcinoma. *B* shows a slight diminution in the mediastinal mass following roentgen therapy. The lesion was essentially radioresistant.

doses can be administered effectively over widespread areas with no harmful effects.

The technic of roentgen therapy for lymphosarcoma and Hodgkin's disease has undergone various changes. When the transition from the lower to the higher voltage was made, massive doses were at first administered which caused many disastrous results. The desirability of fractionating the dose was soon established (Dresser,<sup>24</sup> Desjardins,<sup>25</sup> Voorhoeve<sup>26</sup> and Gilbert and Sluys<sup>27</sup>). The other development of importance was the recognition that the actual distribution of the disease is nearly always wider than the clinical examination discloses, and consequently wide areas must be irradiated in which the presence of the disease, though not clinically demonstrable, must be suspected.

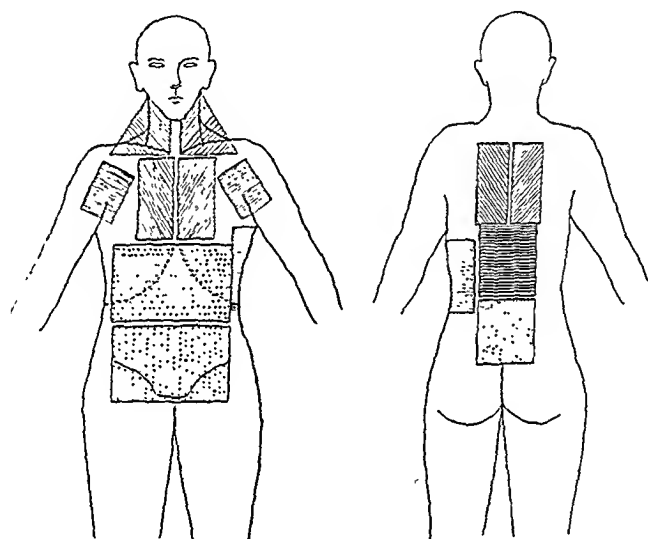


Fig. 26.—A diagram showing the lymph node areas to be treated in cases of lymphosarcoma (Gilbert and Sluys).

Gilbert and Sluys<sup>27</sup> elaborated a technic of roentgen therapy for malignant granuloma which has yielded interesting results.

24. Dresser, R.: Lymphoblastoma (Hodgkin's Disease) of Sternum, *Am. J. Roentgenol.* **15**:525 (June) 1926; Lymphogranulomatose der Knochen (Hodgkinsche Krankheit), *Strahlentherapie* **41**:401, 1931.

25. Desjardins, A. U.: Radiotherapy for Lymphoblastoma, *Radiology* **7**:121 (Aug.) 1926; Rationale of Radiotherapy in Hodgkin's Disease and Lymphosarcoma, *Am. J. Roentgenol.* **17**:232 (Feb.) 1927.

26. Voorhoeve, N.: La lymphogranulomatose maligne; résultats obtenus par l'auteur avec la röntgentherapie; les principes du traitement et leur application; Valeur de la biopsie pour le diagnostic, *Acta radiol.* **4**:567, 1925. On Granuloma Malignum, *ibid.* **5**:374, 1926.

27. Gilbert, R., and Sluys, F.: La radiothérapie de la granulomatose maligne, *J. de radiol. et d'électrol.* **17**:129 (March) 1933.

Figure 26 shows the fields which Gilbert and Sluys utilized. The factors were as follows: from 180 to 200 kilovolts, intensity of from 2 to 4 milliamperes and filtration with from 0.5 to 1 mm. of copper with the focal distance varying with the depth of the lesion and the

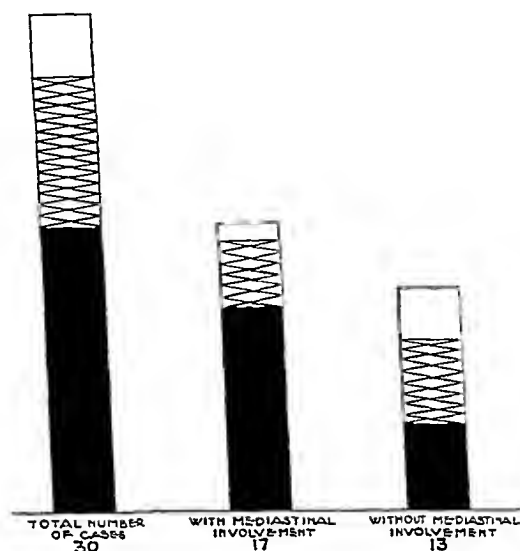


Fig. 27.—A chart showing the present condition of the patients with lymphosarcoma. The solid black areas indicate the number of patients who died; the cross-hatching, the number who are alive, but show evidence of the disease, and the white areas, the number who are living and are without symptoms.

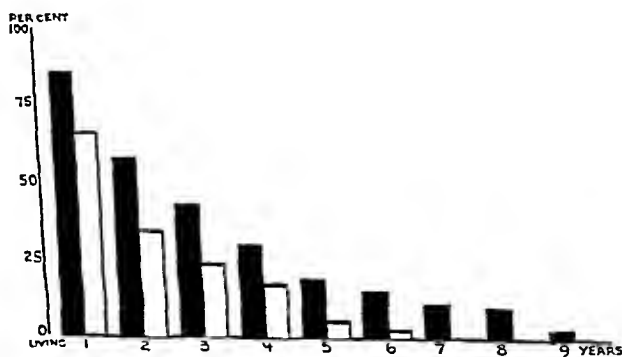


Fig. 28.—A chart showing the duration of the disease from the onset of symptoms in cases of Hodgkin's disease and lymphosarcoma. The black areas indicate the number of patients with Hodgkin's disease, and the white areas, the number with lymphosarcoma.

size of the field. The dose to each field in the first series was 400 r (roentgen). For the more superficial lesions in the cervical and axillary nodes the total dose was between 700 and 1,100 r. For mediastinal

lesions a dose of 1,000 r was administered to each of four portals, making a total of 4,000 r. The patient was treated daily, receiving 170 r at each treatment. When the lesion was extensive the dose during the first few days was diminished in order to avoid a toxic reaction. The treatment was continued once or twice a day for from four to five weeks. In certain cases in which the lesions proved to be resistant to roentgen therapy a response to distance massive radium therapy has been noted (Bowling,<sup>28</sup> Mallet<sup>29</sup> and Dautwitz<sup>30</sup>).

TABLE 2.—*Condition of Patients with Lymphosarcoma on Feb. 1, 1934*

	Mediastinal Involvement	Without Mediastinal Involvement	Total	Per Cent of Total
Alive, with symptoms.....	4	5	9	30
Alive, without disease.....	1	3	4	13
Deceased.....	12	5	17	57
Total.....	17	13	30	100

TABLE 3.—*Interval from the Onset of the Disease to Death in Cases with Fatal Outcome\**

Duration, Months	Mediastinal Involvement	Without Mediastinal Involvement	Total
0 to 6.....	4	0	4
7 to 12.....	3	2	5
13 to 18.....	3	0	3
19 to 24.....	0	1	1
25 to 30.....	0	1	1
31 to 36.....	0	1	1
37 to 42.....	0	0	0
43 to 48.....	0	0	0
49 to 54.....	1	0	1
Total.....	11	5	16

\* One case could not be included in the study regarding duration, since death was caused by suicide.

With some exceptions I have utilized the principle of irradiating not only the lesions that are clinically evident but all lymph node areas which do not show clinical evidence of disease but which are regarded as potentially invaded. Irradiation is given daily for four or five weeks.

28. Bowling, H. H.: Value of Radium and X-Ray Therapy in Hodgkin's Disease, *J. Radiol.* 2:20 (Dec.) 1921.

29. Mallet, L.: Curiethérapie: Technique physique et posologie: Application aux principaux cancers, Paris, J. B. Baillière et fils, 1930, p. 300.

30. Dautwitz, F.: Lymphogranulomatose und Radiumbestrahlung, *Strahlentherapie* 25:375, 1927.

## RESULTS

The length of time that elapsed between the onset of symptoms and the beginning of treatment in this series of cases varied from one month to three years, the average interval being ten months. In 17 of the 30 patients there was roentgenologic evidence of mediastinal involvement, and in 13 the mediastinum appeared to be normal. Table

TABLE 4.—Interval from the Onset of the Disease to Feb. 1, 1934, in Cases in Which the Patients Are Living

Duration, Months	Mediastinal Involvement	Without Mediastinal Involvement	Total
7 to 12.....	1	0	1
13 to 18.....	1	1	2
19 to 24.....	1	3	4
25 to 30.....	0	0	0
31 to 36.....	0	0	0
37 to 42.....	1	0	1
43 to 48.....	0	1	1
49 to 54.....	0	2	2
55 to 60.....	0	0	0
61 to 66.....	0	0	0
67 to 72.....	0	1	1
73 to 78.....	0	0	0
79 to 84.....	1	0	1
Total.....	5	8	13

TABLE 5.—Interval from the Onset of the Disease for All Patients Living and Dead

Duration, Months	Mediastinal Involvement	Without Mediastinal Involvement	Total
0 to 6.....	4	0	4
7 to 12.....	4	2	6
13 to 18.....	4	1	5
19 to 24.....	1	4	5
25 to 30.....	0	1	1
31 to 36.....	0	1	1
37 to 42.....	1	0	1
43 to 48.....	0	1	1
49 to 54.....	1	2	3
55 to 60.....	0	0	0
61 to 66.....	0	0	0
67 to 72.....	0	1	1
73 to 78.....	0	0	0
79 to 84.....	1	0	1
Total.....	16	13	29

2 and figure 27 show the condition at the time of writing of the patients with and those without mediastinal involvement.

## DURATION OF LIFE

The period from the onset of symptoms to death or, in the case of patients still alive, to Feb. 1, 1934, ranged from two months to six years and eight months. In the cases with fatal outcome the minimum period of survival was two months and the maximum, four years and



five months. The average or mean period was approximately sixteen months (table 3).

For the patients alive on Feb. 1, 1934, the minimum interval from the onset of symptoms was ten months and the maximum, six years and eight months. The average interval was three years (table 4).

If one includes all patients both deceased and living, the average interval from the onset of symptoms to death or to Feb. 1, 1934, was twenty-five months, or approximately two years (table 5).

A study of 100 patients with Hodgkin's disease is at present under way, and it seemed interesting to compare the data relating to the duration of the disease in that group with the duration in the group with lymphosarcoma. It is evident from table 6 and figure 28 that patients suffering from Hodgkin's disease live somewhat longer than those suffering from lymphosarcoma.

TABLE 6.—*Comparative Figures on Interval from the Onset of the Disease to Death or to Feb. 1, 1934, in Cases of Hodgkin's Disease and of Lymphosarcoma*

	Lymphosarcoma		Hodgkin's Disease	
	Cumulative Frequency	Per Cent	Cumulative Frequency	Per Cent
Alive				
0 to 3 months.....	29	100	80	100
4 to 6 months.....	28	97	80	100
7 to 12 months.....	25	86	80	100
13 to 24 months.....	19	66	69	86
25 to 36 months.....	10	34	46	58
37 to 48 months.....	7	24	34	43
49 to 60 months.....	5	17	24	30
61 to 72 months.....	2	7	15	19
73 to 84 months.....	1	3	12	15
85 to 96 months.....	0	0	9	11
97 to 108 months.....	0	0	8	10
109 to 120 months.....	0	0	2	3

#### COMMENT

Lymphosarcoma can be divided into two major clinical groups: (1) a generalized form, with widespread involvement of the lymph nodes, and (2) a localized form, in which a single group of lymph nodes or a localized area of lymphoid tissue is the seat of the disease. The generalized form is more common, the localized form comparatively rare. In my group of 30 cases the ratio was 5:1 (25 of the diffuse form and 5 of the localized form).

The generalized form of the disease usually attacks the superficial and deep lymph nodes throughout the body. Sometimes the mediastinal nodes are extensively invaded, giving rise to a large mediastinal tumor. In this series of 30 cases 17 patients, or 56 per cent, showed roentgenologic evidence of mediastinal disease, and among 13 cases which came to autopsy, gross and microscopic evidence of mediastinal involvement was seen in 9. The absence of positive roentgenologic evidence of mediastinal involvement does not necessarily indicate the absence of

disease, and in view of the high percentage of involvement in the mediastinal nodes as proved by autopsy, this area must be regarded as potentially involved and must be treated accordingly.

The same principle holds true for the retroperitoneal and mesenteric regions. The lymph nodes of these regions proved to be involved in 11 of the 13 patients who were examined at autopsy (85 per cent), with involvement of the retroperitoneal glands in 8 and of the mesenteric glands in 3. This circumstance renders it essential to regard the mesenteric and retroperitoneal areas as potentially involved, and they must be treated accordingly regardless of the absence of the disease on clinical examination.

The localized form of the disease occurred in 5 patients. In 2 the disease originated in the nasopharynx and extended upward to the accessory sinuses. Both died; at autopsy no other evidence of disease was discovered in 1, and the second patient died without showing other clinical evidence of disease. Two patients with lymphosarcoma of the rectum are well after two years and three years, respectively, without showing further evidence of the disease at any time. The fifth patient was treated two years ago for a mass of nodes localized in the left cervical region. The lesion disappeared under irradiation, and there has never been evidence of the disease in any of the other lymphoid structures.

When the mediastinum shows extensive involvement, the clinical and roentgenologic features are such as to simulate tumors of thymic origin. The histogenesis of the thymic parenchyma being undetermined, it is not feasible to classify these tumors. Some authors divide thymic tumors into lymphosarcoma and carcinoma; others designate the whole group by the term thymoma. Regardless of their histogenesis, however, one fact is certain: From the point of view of radiosensitivity they form two distinct and separate groups. One is highly radiosensitive and the other markedly radioresistant.

The radiosensitive forms comprise two histologic types: (1) the small round cell type, or malignant lymphocytoma, and (2) the large round cell type, or reticulum cell lymphosarcoma. The small cell type is exceedingly rare. According to Haagensen<sup>22</sup> it occurs usually in children, occupies the thymic region and metastasizes widely. The large round cell type occurs much more frequently. The histogenesis of this type is disputed, some believing that it arises in the anterior mediastinal lymph nodes and others that it originates in the thymus.

The radioresistant thymic tumors present a varied histologic structure. In some the cells are large and flat, in some places forming structures which resemble Hassall's bodies. In others the cells are arranged in alveoli and present a definite glandular structure. In most examples the structure is mixed, and one finds alveolar areas, polyhedral cells and

lymphocytes enmeshed in a dense connective tissue stroma. In some tumors the cells lining the alveoli are cylindric (fig. 11).

The difference in the radiosensitivity of the two groups of mediastinal tumors intimately connected with the thymus is so striking that a moderate dose of external radiation constitutes a valuable therapeutic test in differentiating between the two forms.

The principles of treatment of lymphosarcoma differ for the generalized and localized forms. In the case of the generalized form, wide areas are exposed to radiation and all areas bearing lymph nodes are treated, regardless of the distribution of the disease that is evident on clinical examination. In view of the extensive areas of the body that must be exposed to radiation and because of the marked radiosensitivity of the lesion, the doses over each portal of entry are relatively small compared to those utilized in the treatment of the epidermoid carcinomas. The rapidity with which the exposures are made is guided by the general condition of the patient.

The principle of treatment of the localized form differs from that for the generalized form. Because of the limited extent of the disease, it is safe to deliver a much larger dose of radiation. Although under these circumstances it is not necessary to simulate the large doses used in the treatment of carcinoma, the dose should be much larger than that which can be administered safely in cases of the generalized form of the disease. Thus, for example, the patient with a localized mass of cervical lymph nodes and no other clinical evidence of disease received 80,000 mg. hours of radium at a distance of 10 cm. over a surface area 10 cm. in diameter during a period of three weeks.

The question naturally arises as to the differentiation of the localized from the generalized forms of the disease when only a single focus can be detected on clinical examination. I know of no method by which it can be predicted that the appearance of a localized focus of the disease will or will not be followed by the appearance of the disease in other areas. This difficulty raises the important question of whether it may not be an expression of sound judgment to irradiate prophylactically all lymphoid areas regardless of how limited the disease may appear to be on clinical examination. No general rule can be made on this point, but each case should be considered on an individual basis with these facts in mind.

The results of roentgen therapy of lymphosarcoma may be summarized briefly. In the generalized form the disease may be arrested for varying periods and may sometimes be controlled for several years. In the rare localized forms the disease can be eradicated. This result is sometimes followed by the appearance of the disease elsewhere in the body, but occasionally an apparent cure can be accomplished, the patient remaining well and free from the disease for as long as ten years.

## SUMMARY AND CONCLUSIONS

Thirty cases of microscopically proved lymphosarcoma are reported.

Thirteen patients died in the hospital, and all came to autopsy. The pathologic observations are presented.

Seventeen, or 57 per cent of the group, are dead. The minimum duration of life from the onset of symptoms to death was two months, the maximum duration, four years, and the average duration, sixteen months.

Of the 13 patients alive 9 show clinical evidence of the disease and 4, or 13 per cent, show no evidence of the disease.

For the patients alive, the minimum interval from the onset of symptoms to Feb. 1, 1934, was ten months, the maximum, six and one-half years and the average, three years.

Including all cases, the average interval from the onset of the disease to death or to Feb. 1, 1934, was approximately two years.

For the 4 patients who are alive and clinically free from the disease, the interval of freedom from the disease varies between two and six years.

Twenty-three of the 28 patients treated by irradiation, or approximately 80 per cent, were benefited by the treatment. Regression of the tumors, relief from the pain and improvement in the general condition of the patient constituted the immediate primary results following treatment.

The disease has a notorious tendency to recur, and more particularly to reappear in outlying areas. Prophylactic irradiation to lymph node areas which are not clinically involved may help to diminish this tendency. There is some evidence that the pursuit of this principle has averted the danger in some instances.

# NEUROFIBROMA OF THE URETER

REPORT OF A CASE WITH OPERATION AND RECOVERY

A. RAVICH, M.D.

BROOKLYN

When one considers the ureter merely as a muscular duct which transmits the urine secreted and excreted by the kidney into the bladder, it is not surprising that one finds so few instances of primary tumor of this organ. The majority of the neoplasms involving the ureter are papillary carcinomas which originate in the pelvis of the kidney and the cells of which break off and implant themselves on the mucosa of the ureter. Whereas benign papilloma occurs rather infrequently in the pelvis of the kidney, it is still rarer for such a growth to spread secondarily along the ureter until after it has become malignant. Primary carcinoma of the ureter is also rare, only sixty-one cases having been reported in the literature.

Careful perusal of the literature failed to reveal a single case analogous to the one here reported, even though involvement of almost every other organ in the body by this type of tumor had been reported by various authors.

## REPORT OF CASE

J. B., an Italian stevedore, aged 50, married, was referred by Dr. Bendetson on Nov. 20, 1930. The history was unessential except for uncomplicated gonorrheal urethritis ten years before. Several months previously he began to have slight backache, principally on the left side. For the preceding four weeks the patient had considerable pain in the left iliac region radiating down to the groin and testis and upward to the left flank. The pain was more or less constant, but was worse at night and frequently severe enough to keep him awake. At times he had attacks of fairly severe pain, but never severe enough to require a hypodermic injection. There were no urinary disturbances except nocturia two or three times. There was no macroscopic hematuria, although urinalysis revealed a few erythrocytes.

Physical examination revealed a swarthy, well nourished, obese and muscular man. The heart sounds were distant but of fairly good quality. There was slight tenderness over the left costovertebral region and, on deep palpation, in the left lower quadrant. No masses could be felt.

The bladder urine showed a specific gravity of 1.018, was clear, gave a positive reaction for acid and albumin and a negative reaction for sugar and contained a rare erythrocyte, an occasional leukocyte, a rare hyaline cast and an occasional epithelial cell. It contained no bacteria.

On examination by rectum the prostate was practically normal. Roentgen examination revealed both kidneys to be slightly enlarged, though the outlines were not very clear owing to the large size and muscularity of the patient. No

calculi were seen in the urinary tract. After careful study, on the left side of the spine above the iliac crest a faintly outlined, irregular shadow the size of a tangerine was seen, the nature of which could not be determined.

Cystoscopy revealed a definite lip formation of the median lobe of the prostate and normal lateral lobes, and also a normal bladder mucosa. The orifice of the right ureter was normal; that of the left was slightly injected. Indigo carmine, injected intravenously, appeared in five minutes from the right orifice; none had appeared at the end of ten minutes from the left. A no. 6 F wax-tipped catheter was passed up the left ureter, meeting marked obstruction 15 cm. and an impassa-

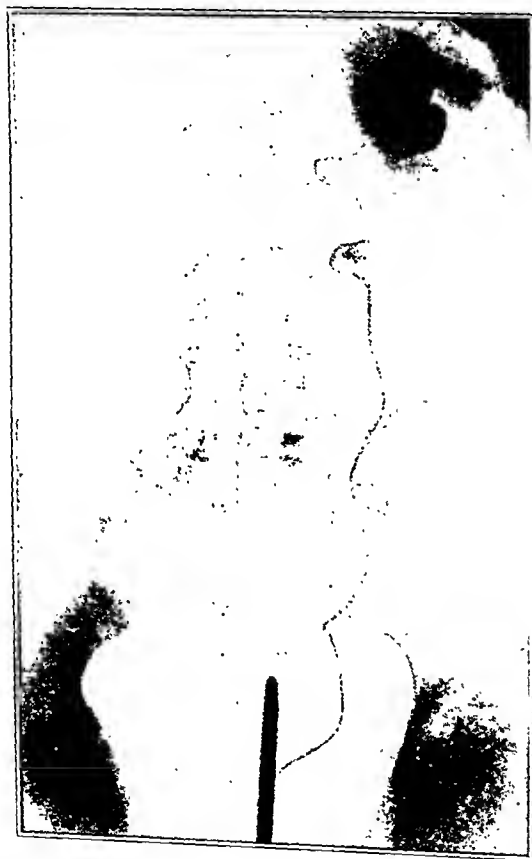


Fig. 1.—Retrograde pyelogram showing the dilated renal pelvis, dilatation and kinking of the upper portion of the ureter and the tip of the catheter obstructed at the upper margin of the tumor, which extends around the ureter from the third lumbar vertebra down to the sacro-iliac synchondrosis. Note the apparent failure to visualize the lower calix.

ble obstruction 24 cm. from the bladder. No scratch was seen on the wax tip. Later a no. 5 F catheter was passed and met the same impassable obstruction at 24 cm. A left retrograde pyelogram (fig. 1) revealed a markedly dilated renal pelvis with obliteration of the calices and a possible filling defect or failure to outline the lower calix and lower quarter of the pelvis, giving the impression of a mass involving the lower pole of the left kidney. The upper 6 cm. of the ureter was kinked and dilated to the size of a finger. Below this the ureter was

very narrow and showed a slight angulation at the lower level of the synchondrosis. The inferior margin of the mass in the film corresponded to the obstruction met by the catheter 15 cm. from the bladder. No urine was obtained from the left kidney.

A diagnosis of tumor of the left ureter secondary to a possible intrapelvic tumor was made, and nephro-ureterectomy was advised.



Fig. 2.—Cross-section showing the dilated renal pelvis and calices and also the large tumor surrounding the ureter. Note the dilated portion of the ureter at the upper border of the neoplasm, which narrows rapidly as it runs through the mass.

Two days later the patient entered the Jewish Hospital of Brooklyn, where, on November 24, intravenous pyelography showed a fairly normal right renal pelvis and ureter, but no dye was seen in the left renal pelvis or ureter. A mass of soft tissue the size of a tangerine was noted opposite the fourth lumbar vertebra.

A blood count showed: 7,300 leukocytes, 4,750,000 erythrocytes and 70 per cent hemoglobin. Chemical examination of the blood showed: sugar, 122 mg. per hundred cubic centimeters; creatinine, 2 mg.; urea nitrogen, 22.8 mg., and uric acid, 6 mg. The phenolsulphonphthalein test showed an excretion of 52 per cent for the first hour and 32 per cent for the second hour, making a total output of 84 per cent. The reactions to the Wassermann and Kahn tests were negative. The blood pressure on admission was 170 systolic and 110 diastolic.

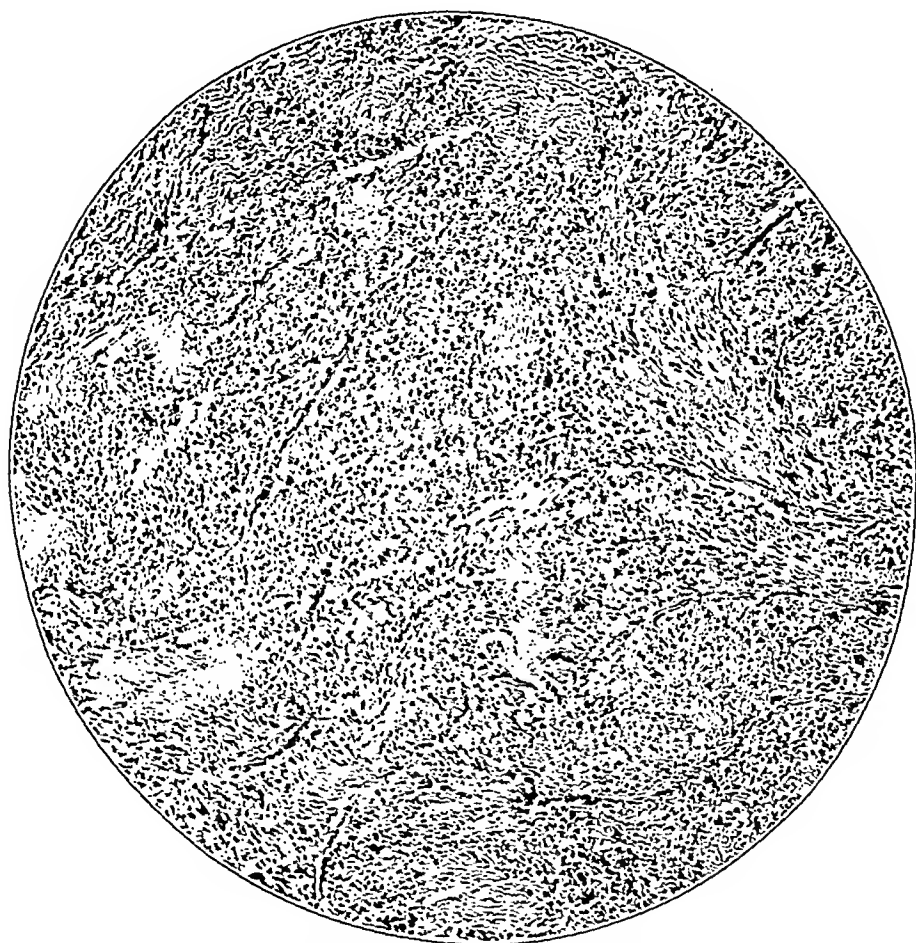


Fig. 3.—A section showing the arrangement of the fibers in irregular bundles. Hematoxylin-eosin stain;  $\times 100$ .

On November 26, with the patient under spinal anesthesia later reenforced by a small quantity of ether, a hockey stick incision was made over the left kidney from the costovertebral angle to the anterior iliac portion of the spine. The kidney was mobilized and found to be slightly enlarged, smooth, anemic, distended and thinned out in several areas. The pelvis and the upper 8 cm. of the ureter were very thin and distended with urine. The upper part of the ureter was the size of a thumb. The vascular pedicle, which was somewhat elongated but otherwise normal, was clamped, tied and cut. The ureter was followed downward below the dilated portion, where it was found to run directly into the middle of a large,



irregular, stony-hard mass the size of a tangerine, which was so adherent to the adjacent tissues by thick bands and adhesions that it was finally freed with the greatest difficulty and excised after each band was clamped and tied. The ureter was clamped, tied and severed below the mass. The peritoneum was carefully avoided. The wound was then closed in layers around two cigaret drains.

Except for some abdominal distention, oliguria and slight elevation of temperature for several days, the postoperative course was smooth. The blood pressure



Fig. 4.—A section showing the nerve fibers. Silver stain;  $\times 100$ .

during the three days following operation ranged between 110 and 140 systolic. The blood urea nitrogen and creatinine values were 62.4 and 3.1 mg., on December 1, and 27.7 and 2 mg. on December 4. Owing to a slight cardiac disturbance the patient was kept in bed until December 9, the fourteenth day after operation. The wound healed by primary union, and the patient was discharged on December 13 in good condition.

The pathologic report was made by Dr. M. Lederer. Macroscopically the left kidney weighed 120 Gm. The capsule stripped off easily, and the surface was smooth except for many small cysts containing clear fluid. The surface was

mottled red, and one area was depressed. A section showed a diffusely yellow appearance. The normal renal tissue had been replaced by numerous dilated sacs (fig. 2).

The normal line of demarcation between the cortex and the medulla was absent. In some areas the renal tissue measured only 3 cm. in width. The pelvis was infiltrated by yellow tissue and was greatly dilated and thin. Microscopically the kidney showed the usual lesions of hydronephrosis.

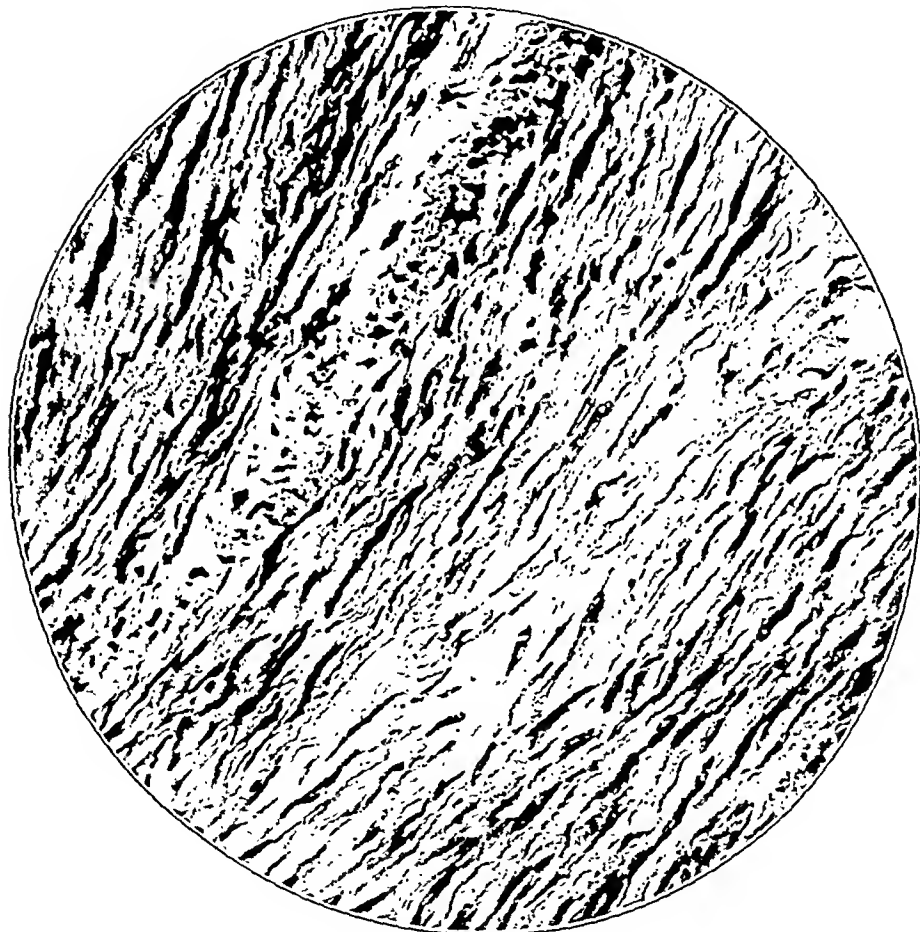


Fig. 5.—The same section as that shown in figure 4;  $\times 450$ .

Macroscopically the ureter was surrounded by an irregular mass, 8 cm. in its longest diameter, which completely constricted the lumen of the ureter. From the surface of the mass projected several smaller nodules, each about 2 cm. in diameter, which on section were shown to be made up of dense yellow-gray tissue. The main mass was directly continuous with the ureteral wall, which was thinned both above and below the involving tumor. The major portion of the ureteral wall was markedly embedded in the surrounding mass of interlacing bundles of gray tissue, so that it could not be dissected from the latter.

Microscopically the tumor was made up of numerous bundles composed of interlacing fibers. The fibers gave a positive reaction on staining for nerve cells. The arrangement of the cells was in large masses separated from each other by a small amount of connective tissue stroma. In some areas the cells assumed large proportions, resembling nerve cells (figs. 3, 4 and 5).

The diagnosis was neurofibroma of the ureter.

#### CONCLUSION AND SUMMARY

This unique case is presented for the following reasons: 1. Primary tumors of the ureter are very rare. 2. No tumor of this kind involving the ureter has been found reported in the literature.

Correct preoperative diagnosis of the tumor was made by means of a wax-tipped catheter and by a retrograde pyelogram. The erroneous impression of a concomitant pelvic tumor was created by the pelvic outline, which showed an irregular mass in the lower portion of the renal pelvis.

This case demonstrates the futility of the present-day tendency among many physicians to depend entirely on intravenous pyelography for the diagnosis of all pathologic conditions of the urinary tract.

There was an amazing freedom from symptoms until a short time before the operation in spite of the fact that the large tumor had been gradually increasing its encroachment on the ureteral lumen, with destruction of the kidney parenchyma.

The success of early operation is apparent. The patient was alive and well in January 1934, when last heard from through Dr. Bendetson.

The general practitioner should be as suspicious of vague urologic conditions as he is of a pathologic condition in the breast. It is only through early diagnosis and treatment that satisfactory results can be hoped for.

101 Lafayette Avenue.

# CHOLECYSTOGASTROSTOMY AND HEPATITIS

## AN EXPERIMENTAL STUDY

ANTONIO GENTILE, M.D.

NEWPORT NEWS, VA.

Increased interest in surgical intervention on the gallbladder has resulted in the removal of cholecystogastrostomy from the class of serious, much feared and seldom performed operations to that of operations which are considered less serious and with which every surgeon has had experience. Its wider use has been hindered by a fear that infection of the liver may occur as a sequel. Many investigators have tried both experimentally and clinically to avoid this and other sequelae. This study is an experimental attack on the problem of hepatic infection following cholecystogastrostomy from a new point of view. Some light is thrown on the general pathologic problem of hepatic infection.

## REVIEW OF THE LITERATURE

Experimentally, the gallbladder has been anastomosed to the alimentary tract at various points of the stomach, duodenum, jejunum and colon. Many studies have been made to determine which method will yield as nearly a physiologic result as possible and avoid undesirable accompaniments of such a procedure. The first cholecystenterostomy was done by von Winiwarter<sup>1</sup> of Liege; it was a short-circuiting operation which consisted in joining the gallbladder to the colon in seven stages over a period of sixteen months (from 1880-1881).

Oddi<sup>2</sup> (1887), in his study of the effect of bile on gastric acidity, performed perhaps the first cholecystogastrostomy experimentally, using the dog. He came to the conclusion that bile in the stomach before or after digestion does not affect the acidity or diminish the quantity of gastric juices. He observed that bile caused no alterations of the gastric content. He prophesied the use of cholecystogastrostomy in certain cases of disease of the gallbladder. Dastre<sup>3</sup> (1890), Cannac<sup>4</sup> (1897),

---

From the Department of Surgery and Gynecology, University of Virginia School of Medicine, University, Va.

1. von Winiwarter, A.: Ein Fall von Gallenretention bedingt durch Impermeabilität des Ductus choledochus. *Anlegung einer Gallenblasen-Darm Fistel, Heilung*. Prag. med. Wchnschr. 7:201 and 213, 1882.

2. Oddi, R.: Action de la bile sur la digestion gastrique étudiée au moyen de la fistule coléocisto-gastrique. *Arch. ital. de biol.* 9:138, 1888.

3. Dastre, A.: Recherches sur la bile. *Arch. de physiol. norm. et path.* 2: 315, 1890.

4. Cannac, L. D.: De la cholécystogastrostomie. Thèse de Bordeaux, 1897, p. 62.

Masse <sup>5</sup> (1898) and Beaver <sup>6</sup> (1929) performed similar experiments and arrived at the same conclusion in relation to the gastric content. Beaver also found that the emptying time of the stomach following cholecystogastrostomy was the same as in the normal dog. Mocquot <sup>7</sup> (1911), Wiedemann <sup>8</sup> (1914) and Grey <sup>9</sup> (1916) performed cholecystogastrotomies and investigated the effect of bile on gastric digestion. The unanimous conclusion was that bile does not affect gastric digestion. In view of the newer ideas in regard to the interchange of duodenal and gastric content, the presence of bile in the stomach of a normal person is now accepted, and the discharge of bile into the stomach following cholecystogastrostomy is therefore not regarded as an important physiologic distortion. Beaver <sup>6</sup> and Grey <sup>9</sup> studied separately the acidity of gastric juice before and after this operation, and both found that bile in no way affects the gastric acidity. Bogoras <sup>10</sup> (1925) advocated the use of cholecystogastrostomy as a means of controlling gastric acidity by allowing the bile to flow into the stomach. Following the work of Graham <sup>11</sup> (1918), in which he showed rather conclusively that hepatitis is a constant accompaniment of cholecystitis, Gatewood and Poppens <sup>12</sup> (1922), Lehman <sup>13</sup> (1924) and Horsley <sup>14</sup> (1927) studied the effect on the liver and the biliary tract of cholecystogastrostomy. In his experiments Lehman attempted to remove all lymphatic connections between the liver and the gallbladder. All of these authors concluded that the liver and biliary tract always became infected in the dog following this operation. Weinberg, Wallin and Binger <sup>15</sup> (1927) found

5. Masse, E.: De la cholecystogastrostomie, *Gaz. hebdomadaire de médecine et de chirurgie*, 1898, 19:534.

6. Beaver, M. G.: Cholecystogastrostomy: An Experimental Study, *Arch. Surg.* 18:899 (March) 1929.

7. Mocquot, Pierre: Anastomose de la vésicule biliaire avec l'estomac et avec le duodénum, *Compt. rend. Soc. de biol.* 2:118, 1911.

8. Wiedemann, H.: Experimentelle Untersuchungen zur Lehre der Verdauung und Resorption verschiedener Nahrungsprodukte bei anormalen Gallenzufuss in den Verdauungsapparat, *Beitr. z. klin. Chir.* 74:594, 1914.

9. Grey, E. G.: An Experimental Study of the Effect of Cholecystogastrostomy on Gastric Acidity, *J. Exper. Med.* 33:15, 1916.

10. Bogoras, N.: Cholecystogastrostomy in Gastric Ulcer; Operative Method for Treatment of Gastric Ulcer, *Arch. f. klin. Chir.* 134:42, 1925.

11. Graham, E. A.: Hepatitis: A Constant Accompaniment of Cholecystitis, *Surg., Gynec. & Obst.* 26:521, 1918.

12. Gatewood, and Poppens, P. H.: Cholecystenterostomy from an Experimental Standpoint, *Surg., Gynec. & Obst.* 35:445, 1922.

13. Lehman, E. P.: Hepatitis, Following Cholecystogastrostomy, *Arch. Surg.* 9:16 (July) 1924.

14. Horsley, J. S., Jr.: Experimental Study of Cholecystogastrostomy and Cholecystoduodenostomy, *South. M. J.* 20:669, 1927.

15. Weinberg, J. A.; Wallin, S. P., and Binger, M. W.: Gallbladder-Stomach Anastomosis, *Surg., Gynec. & Obst.* 44:795, 1927.

hepatic infections invariably in dogs but not in a single monkey after cholecystogastrostomy.

It was not long after Oddi<sup>2</sup> suggested the use of cholecystogastrostomy in disease of the gallbladder that it was used clinically. As early as 1889, Mayo-Robson<sup>16</sup> performed what is now regarded as perhaps the first cholecystogastrostomy. However, the first cholecystogastrostomy with survival of the patient was done for stricture of the common bile duct in 1892 by Wickhoff and Angelberger<sup>17</sup> of Vienna, who thus furnished the first clinical data as to the tolerance of the stomach for bile. About this time Terrier<sup>18</sup> and Bardenheurer,<sup>19</sup> at the suggestion of Cozi, first used the duodenum in a short-circuiting operation to join the gallbladder to the intestinal tract.

Cholecystogastrostomy was performed by Terrier<sup>18</sup> (1896), Monod<sup>20</sup> (1896), Jaboulay<sup>21</sup> (1898) and Montognon and Duchamp<sup>22</sup> (1899) with favorable results in cases of tumors of the pancreas. Perrin<sup>23</sup> (1902) advocated the operation because of its nearness to anatomic and physiologic perfection as well as because of its simplicity. Eichmeyer<sup>24</sup> (1910) and Kohr<sup>25</sup> (1914) had early favorable experiences with the procedure, the latter having up to 1914 performed over sixty operations and published the reports of over one hundred. Jacobson<sup>26</sup>

16. Mayo-Robson, A. W.: A Case of Cholecystenterostomy, *Med.-Chir. Tr.*, London **73**:61, 1890.

17. Wickhoff, M., and Angelberger, F.: Cholelithiasis; Obdurater Ductus Choledochi(?) Cholecysto-Gastrostomie, Heilung, *Wien. klin. Wchnschr.* **6**:325, 1893.

18. Terrier, M.: Sur un cas de gastrocystentérostomie, *Bull. et mém. Soc. de chir. de Paris* **22**:565, 1896.

19. Bardenheurer, cited by Moore, C. A.: A Case of Cholecystogastrostomy, *Brit. M. J.* **1**:14, 1921.

20. Monod, M.: Suite de la discussion sur la cholédocotomie, *Bull. et mém. Soc. de chir. de Paris* **22**:546, 1896.

21. Jaboulay, M.: La cholécystogastrostomie pour les tumeurs de la tête du pancreas, *Lyon méd.* **89**:365, 1898.

22. Montognon and Duchamp: Obstruction néoplasique du cholédoque, abouchement de la vésicule dans l'estomac, *Loire méd.* **8**:142, 1899.

23. Perrin, F. H.: La cholécystogastrostomie dans l'occlusion supposée complète et directement irrémédiable du cholédoque, *Thèse de Lyon*, no. 96, 1902, p. 169.

24. Eichmeyer, W.: Beiträge zur Chirurgie des Choledochus und Hepaticus einschliesslich der Anastomosen zwischen Gallen-System und Intestinis, *Arch. f. klin. Chir.* **93**:857, 1910; **94**:1, 1911.

25. Kohr, H.: Die Praxis der Gallenwege-Chirurgie in Wort und Bild, Munich, J. F. Lehmann, 1913, vols. 1 and 2. Die gut- und bösartigen Neubildungen der Gallenblase und der Gallengänge unter besonderer Berücksichtigung eigener Erfahrungen, *Ergeln. d. Chir. u. Orthop.* **8**:471, 1914.

26. Jacobson, J. H.: Anastomosis of the Gallbladder to the Stomach: "Cholecystogastrostomy," *Tr. Am. A. Obst. & Gynec.* **27**:172, 1914.

(1914), Erdmann<sup>27</sup> (1918) and Barr<sup>28</sup> (1914) held the opinion that this operation produces better results than any other when there is a necessity for a biliary short circuit. Jacobson<sup>29</sup> and White<sup>29</sup> (1920) reported its successful use, with particular emphasis on the absence of ascending infection.

In recent years cholecystogastrostomy has been recommended for conditions other than obstruction of the common bile duct. After using it successfully in forty-seven cases, Babcock<sup>30</sup> (1920) advocated it for the control of hyperchlorhydria. In cases of small ulcers he anastomosed the gallbladder directly into the ulcerated areas instead of excising the ulcer or performing a gastro-enterostomy. Babcock<sup>31</sup> (1920-1921) and Heyd<sup>32</sup> (1921) expressed a preference for this operation rather than anastomosis at any point lower than the duodenum because in the case of anastomosis at a higher level there remains the possibility of reabsorption of the bile. Deaver<sup>33</sup> (1925) also favored the operation for this reason. Frenkel<sup>34</sup> found that a decrease of total acidity, especially free hydrochloric acid, was a constant result in his twenty-one patients with ulcers of the stomach and duodenum whom he treated by cholecystogastrostomy and cholecystoduodenostomy. Nazarov<sup>35</sup> (1927) obtained satisfactory results with cholecystogastrostomy in cases of ulcer of the stomach. He observed in four cases in which he had to do a secondary laparotomy that the symptoms of ulcer recurred coincident with constriction of the stoma; he therefore concluded that when a cholecystogastrostomy is performed the stoma should be at least from 2 to 3 cm. in diameter. (Wangensteen<sup>36</sup> [1928] stated the belief that in operations for obstruction of the common duct the chief cause

---

27. Erdmann, J. F.: Obstructive (Malignant) Jaundice: Operative Relief by Cholecystogastrostomy, *Ann. Surg.* **67**:273 (March) 1918.

28. Barr, R. A.: "Cholecystogastrostomy," *J. Tennessee M. A.* **7**:454, 1914-1915.

29. White, C. S.: Cholecystogastrostomy, *Surg., Gynec. & Obst.* **31**:493, 1920.

30. Babcock, W. W.: Control of Hyperchlorhydria and Its Consequences by Cholecystogastrostomy, *M. Rec.* **98**:476 (Sept.) 1920.

31. Babcock, W. W.: Cholecystogastrostomy and Cholecystoduodenostomy, *Am. J. Obst. & Gynec.* **1**:854 (May) 1921.

32. Heyd, C. G.: Cholecystogastrostomy and the Courvoisier Gallbladder, *J. A. M. A.* **77**:339 (July 30) 1921.

33. Deaver, J. B.: Cholecystectomy: External and Internal Cholecystostomy, *Ann. Surg.* **81**:761, 1925.

34. Frenkel, A.: Der Einfluss der Cholecystogastrostomie auf den Magenchemismus beim Magen- und Duodenal-Ulcus, *Zentralbl. f. Chir.* **52**:1459, 1925.

35. Nazarov, N. N.: Cholecystogastrostomy for Gastric Ulcer, *Surg., Gynec. & Obst.* **45**:474, 1927.

36. Wangenstein, O. H.: Cholangitis Following Cholecystenterostomy, *Ann. Surg.* **87**:54, 1928.

of complications is also a narrowing of the stoma.) Braithwaite<sup>37</sup> (1926) stated that in cases of an inaccessible gastric ulcer or an ulcer which is too far removed from the pyloric region to be bathed by regurgitated duodenal juice cholecystogastrostomy is the operation of choice, with a regulated dietary regimen. Thus he agreed with most investigators as to the rôle of bile in the stomach. DuBose<sup>38</sup> (1924) advocated cholecystogastrostomy even in cases of perforated gastric or duodenal ulcer, perforation of the gallbladder and obscure or chronic intermittent jaundice. He stated that the stoma will not close if it is properly made and if the common duct is ligated and divided. Parenthetically, it may be remarked that present knowledge of the portal and lymphatic connections of the organs of the upper part of the abdomen, as pointed out by Sweet,<sup>39</sup> Kodama<sup>40</sup> and others, suggest an important argument against cholecystogastrostomy as the treatment for peptic ulcer. If it is true that a low grade infection in an organ of the upper part of the abdomen may result in or continue a low grade infection in some other organ, then, although one may correct chemical abnormalities in the gastric content due to disturbance of pyloric function, one at the same time exposes the gallbladder to infection, if infection is not already present. The secondarily infected gallbladder may thus perpetuate the conditions that resulted in the original ulcer for which treatment was instituted. These are theoretical considerations, but they must be weighed in accepting the evidence brought forward earlier.

Although the employment of cholecystogastrostomy in the treatment of ulcer is an interesting development, the place of this operation has been almost entirely in the treatment of obstruction of the common bile duct. The clinical literature on this phase is large and need not be reviewed with any completeness. DuBose,<sup>38</sup> White,<sup>39</sup> Heyd,<sup>42</sup> Villard and Richer,<sup>41</sup> Beaver,<sup>6</sup> Erdemann and Heyd,<sup>42</sup> Babcock,<sup>30</sup> Muller,<sup>43</sup>

37. Braithwaite, L. R.: Surgical Treatment of Chronic Duodenal and Gastric Ulcer: Cholecystogastrostomy as the Operation for Inaccessible Gastric Ulcer, *Lancet* 1:900, 1926.

38. DuBose, F. G.: Cholecystogastrostomy and Cholecystoduodenostomy, *Surg., Gynec. & Obst.* 39:295, 1924; Cholecystogastrostomy, *South. M. J.* 22:674, 1927.

39. Sweet, J. E., and Deaver, J. B.: Prepancreatic and Peripancreatic Disease with a Consideration of the Anatomic Basis of Infection from the Gall Bladder to the Pancreas, *J. A. M. A.* 77:194 (July 16) 1921.

40. Kodama, S.: The Lymphatics of the Extrahepatic Biliary Passages, *Surg., Gynec. & Obst.* 43:140, 1926.

41. Villard, E., and Richer: Le cholecysto-gastrostomie, *Rev. de chir., Paris* 63:455, 1925.

42. Erdemann, J. F., and Heyd, C. G.: Relief of Chronic Obstructive Jaundice by Palliative Operation, *Am. J. M. Sc.* 152:174, 1916.

43. Muller, G. P.: Cholecyst-Duodenostomy, *Ann. Surg.* 84:95, 1926.



Walters,<sup>44</sup> Mayo,<sup>45</sup> Moore,<sup>46</sup> Ralphs,<sup>47</sup> Downes,<sup>48</sup> Stretton,<sup>49</sup> McNealy,<sup>50</sup> Murdy<sup>51</sup> and Weinberg, Wallin and Binger<sup>15</sup> reported favorable clinical experiences. The types of lesion for which these operations have been performed include carcinoma of the head of the pancreas, carcinoma of the common duct and the papilla of Vater, chronic pancreatitis with obstruction and obstruction due to anomalies and stricture. Many of these authors emphasized the ease of technical performance, the lack of digestive disturbance and the low mortality. Horsley,<sup>14</sup> on the other hand, reserved cholecystogastrostomy for use as a last resort.

The rationale of cholecystogastrostomy in this connection hardly needs comment. The relief of progressive obstructive jaundice associated with these conditions is of itself a desideratum. The operation prevents progressive hepatic damage from back pressure with an early onset of so-called cholemia. It removes the distressing itching of the jaundiced patient and ordinarily improves the appetite and produces a sense of well-being. It may convert a bedridden, emaciated, somnolent or otherwise distressed person into one who may go about and attend to his affairs. In cases of a disease which in itself is not destructive, such as chronic pancreatitis, a clinical cure may result. In cases of malignant disease the operation is only palliative. In the latter type of case, in which the patient often presents a poor risk, the technical simplicity of the operation recommends it. In cases of stricture of the common bile duct the gallbladder is rarely available because of previous inflammation. If it is available, this operation is to be preferred to hepaticoduodenostomy or implantation of an external fistula because of its relatively low mortality and its simplicity.

In addition to the uses already mentioned, DuBose<sup>38</sup> proposed the employment of cholecystogastrostomy instead of cholecystectomy or cholecystostomy in cases of cholecystitis or cholangitis not due to calculi. This proposition has not been at all widely approved, as it carries with it the fundamental disadvantage that makes cholecystostomy undesirable in the treatment of these conditions, namely, the saving of the

✓44. Walters, W.: Cholecystogastrostomy, *Surg., Gynec. & Obst.* **42**:825, 1926.

45. Mayo, C. H.: Jaundice and Its Surgical Significance, *Surg., Gynec. & Obst.* **30**:545, 1920.

46. Moore, C. A.: A Case of Cholecystogastrostomy, *Brit. M. J.* **2**:826, 1921.

✓47. Ralphs, G.: The Operation of Cholecystogastrostomy, *Brit. M. J.* **1**:14, 1922.

48. Downes, W. A.: Chronic Obstructive Jaundice: A Report of Nine Cases Treated by Cholecystogastrostomy, *Tr. South. S.* **35**:342, 1922.

✓49. Stretton, J. L.: Cholecystogastrostomy, *Brit. M. J.* **2**:600, 1922.

50. McNealy, R. W.: Operative Case: Obstructive Jaundice, *Journal-Lancet* **43**:636 (Dec. 15) 1923.

51. Murdy, R. L.: Indications for Cholecystenterostomy, *Journal-Lancet* **43**:89 (Feb. 15) 1923.

gallbladder, in the wall of which infection lurks. The same may be said of DuBose's<sup>39</sup> proposal to employ cholecystogastrostomy in the treatment of more acute conditions, such as perforation of the gallbladder. In confirmation of these objections one may refer to Deaver's<sup>33</sup> statements that an infected gallbladder never entirely recovers pathologically and bacteriologically, and that a gallbladder that recovers from infection and one that has been the seat of stones invite further infection and the formation of more stones. Illingsworth<sup>52</sup> found bacteria in the walls of gallbladders even in cases in which the bile was found to be sterile. The successful use of this operation in such conditions is not recorded in the literature except by DuBose.<sup>38</sup>

On the basis of evidence, both clinical and experimental, brought forward in the literature and of theoretical considerations already presented, it seems obvious that the present value of cholecystogastrostomy is in the treatment of obstructions of the common duct by the lesions mentioned. This operation should take the place of cholecystostomy only in this type of disease and not in the acute type of disease of the gallbladder for which cholecystostomy is now occasionally performed. It does not seem probable that future experience will suggest its use instead of cholecystectomy for cholecystitis of any type. It must be considered that, in spite of the theoretical disadvantages outlined, the use of cholecystogastrostomy in the treatment of peptic ulcer may be justified with further experience. In cases in which there is a choice of cholecystogastrostomy and external drainage, cholecystogastrostomy is usually to be preferred.

So far the discussion has been limited to questions concerning the value of the method in obstruction of the common duct, irrespective of possible disadvantages. It is obvious that a gallbladder that is the seat of acute cholecystitis, gangrene, hydrops, thickening and contraction or a malignant condition is not suitable for the operation. In the entirely favorable case the question of what physiologic and pathologic disturbances may follow has not yet been settled. All of the evidence so far points to the fact that the gastric function is not disturbed by the discharge of bile into the lumen of the stomach. It is even suggested that a disturbance of gastric function may be corrected in this manner. The point at issue is rather whether or not hepatitis and cholangitis can occur with such frequency and severity as to be a major disadvantage in the use of the operation. The purpose of the present paper is to throw light on this particular phase of the problem.

With the exception of the study of Weinberg, Wallin and Binger<sup>15</sup> and that of Gage<sup>53</sup> (1931), in which there was observed only a slight

52. Illingsworth, C. F. W.: Types of Gallbladder Infection; Study of One Hundred Operated Cases. *Brit. J. Surg.* 15:221, 1927.

✓ 53. Gage, I. M.: Changes in the Liver Following Cholecystogastrostomy and Cholecystoduodenostomy. *Proc. Soc. Exper. Biol. & Med.* 28:693, 1931.

to moderate increase in pathologic findings over the corresponding normal livers, all of the experimental attacks on this problem have shown a tremendous degree of hepatic infection as a result of the operation. In every case dogs were employed. These animals, of course, have a rich bacterial flora in the stomach which is not present in the human stomach. This renders comparison between the dog and the human being fallacious. Although Weinberg, Wallin and Binger<sup>15</sup> obtained the same results in the dog, they found that in a single monkey hepatic infection did not occur. They made no reference, however, to the bacteriologic characteristics of the monkey's stomach.

The clinical literature on cholecystogastrostomy is marked by the fear of this complication. Whether this state of mind has arisen from the aforementioned experimental evidence or whether it has come from actual clinical experience with the occurrence of hepatitis and cholangitis following cholecystogastrostomy is not clear from a reading of the literature. One fact stands out. Although the majority of authors mention the danger, there is a striking paucity of reports showing the incidence of the complication. Nazarov<sup>35</sup> performed secondary laparotomy in four cases in which he had previously performed cholecystogastrostomy for gastric ulcers, but in his report he did not mention the condition of the liver. All of these reoperations were performed for the recurrence of symptoms of ulcer. In the reports of five cases in which he performed a secondary operation, from eight months to five and one-half years after cholecystogastrostomy, Steel<sup>54</sup> stated that the livers were normal to palpation and inspection. No microscopic sections were made. All of Steel's cholecystogastrostomies were performed for obstruction of the common duct. The secondary laparotomies were performed for the recurrence of symptoms, acute appendicitis, pyloric obstruction, incarcerated hernia and epigastric distress. DuBose<sup>36</sup> did not make a microscopic study of the liver in the case in which he performed an operation secondary to cholecystogastrostomy. A thorough search of the literature has not revealed one report of a case in which the presence of hepatitis or cholangitis following cholecystogastrostomy was definitely substantiated by a microscopicopathologic study of sections of the liver removed at operation or at necropsy. It is still more amazing that no cases have been found in which there was a presumptive clinical diagnosis of these sequelae.

In making this statement it is well to differentiate between cholecystogastrostomy and cholecystenterostomy, a distinction which some authors do not clearly make. There are some references to clinical cases of hepatic infection following the latter operation. For example,

---

54. Steel, W. A.: Internal Drainage of Gallbladder as a Routine Operative Procedure, *Surg., Gynec. & Obst.* 44:393, 1927.

Wangensteen<sup>55</sup> cited two cases reported by Kausch<sup>55</sup> in which cholecystojejunostomy was performed for obstructive jaundice and carcinoma of the head of the pancreas. In each of these cases at necropsy suppurative cholangitis was revealed as the cause of death. Gatewood and Lawton<sup>56</sup> reported a case of clinical infection in which at autopsy cholangitis, hepatitis and cirrhosis were found, but they did not state what type of operation was performed.

Except for the mention by Strauss in a discussion of Judd's<sup>57</sup> paper read before the American Medical Association, no reference has been made in the reports of these cases of infection of the biliary tract to the possible presence of the infection before the operation was performed. However, it is safer in this discussion to assume that such infection is the result of operation rather than to attempt to explain it on the basis of a preexisting infection. Yet in any single instance one cannot say that previously present infection may not have been responsible.

It is not wise to assume from this evidence, even if all of the reports had been uncovered in this search of the literature, that cholecystogastrostomy has not been incriminated. On the other hand, in relation to the number of operations of all types which have been performed, the incidence of hepatic infection in the cases reported is unquestionably low. Judd<sup>57</sup> said that "infection is not as apparent clinically as might be expected from a study of gallbladders and livers of experimental animals after the operation." In turn Wangenstein<sup>56</sup> said: "The complication of cholangitis in patients following cholecystenterostomy has only infrequently been observed. Those who have had a considerable experience with the method uniformly agree that the danger of subsequent infection is slight." To judge from the literature, Wangenstein's second sentence is not entirely justified in that a majority of authors refer to infection as a disadvantage to the operation. One wonders, therefore, whether this generally felt fear may not be another of those curious medical traditions that live from textbook to textbook with little justification for their origin.

The present series of experiments was based on an attempt to perform cholecystogastrostomy under conditions in experimental animals simulating those in the human being and thus to obtain results which can be used comparatively with greater safety. The crux of the experimental method was the performance of the operation by the anastomosis

55. Kausch, W.: Ueber Gallenweg-Darmverbindungen. Arch. f. klin. Chir. 97:574, 1912.

56. Gatewood and Lawton, S. E.: The Effect of Cholecystenterostomy on the Biliary Tract. Surg., Gynec. & Obst. 1:40 (Jan.) 1930.

57. Judd, E. S.: "Sidetracking" Operations in Obstructive Jaundice. J. A. M. A. 91:300 (Aug. 4) 1928.

of the dog's gallbladder with its stomach after rendering the stomach relatively free from bacteria. This was accomplished, in brief, by creating a gastric pouch separated from the food current for a considerable time before the anastomosis, as will be detailed later (fig. 1). After the initiation of these experiments it was found that the same principle had been suggested and employed clinically by Monprofit<sup>58</sup> Kausch<sup>55</sup> and Cholin.<sup>59</sup> These operations were in general cholecystojejunostomies performed in a manner resembling Roux's gastroenterostomy in Y.

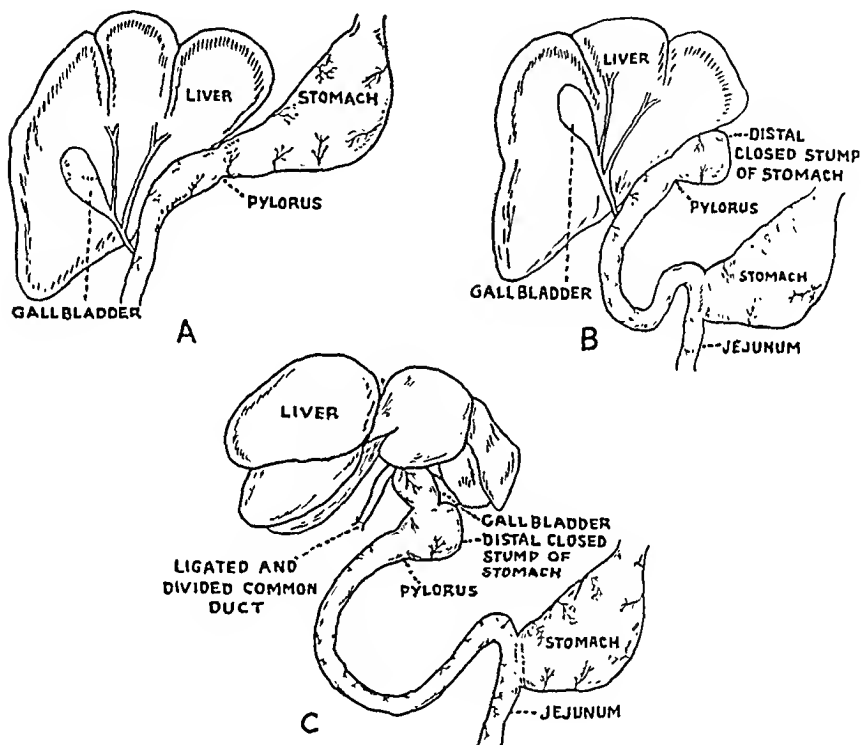


Fig. 1.—Sketches of the operative procedures: *A*, the normal relationships in the dog; *B*, the first stage operation of gastric division and gastrojejunostomy, showing the formation of the gastric pouch, and *C*, the second stage operation of cholecystogastrostomy, the previously prepared gastric pouch being used.

#### METHOD

In the following experiments forty dogs were used without selection as to weight, sex or breed. The dogs were fed the routine laboratory maintenance diet, which consisted of purina chow, meat scraps and oatmeal mash. Food was withheld from the animals for twelve hours before each operation. For thirty-two dogs the anesthetic used was sodium amytal, 0.05 Gm. per kilogram of body

58. Monprofit, A.: On Cholecystenterostomy in the Form of a "Y," Brit. M. J. 2:991, 1908.

59. Cholin, N. K.: Zur Technik der Cholecystoenterostomie, abstr., Zentralbl. f. chir. 36:1769, 1909.

weight in a 10 per cent solution. This was administered in all instances intraperitoneally. In all except a few animals the anesthesia was satisfactory. In three of the thirty-two animals ether was necessary to secure proper relaxation. Three animals failed to recover from the anesthesia. Death was attributed to a possible error in the dosage. Eight dogs were given only ether.

All of the following operative procedures were performed under strictly aseptic precautions. The clean-shaven abdomen of the animal was washed with soap and water and then with iodine, 3 per cent, and alcohol, 95 per cent, as a preparation of the operative field. The abdominal closure was effected in all instances as follows: Linen thread was used for the peritoneum, no. 1 chromic catgut for the fascia, and linen thread for the skin.

The procedures may be divided into two groups: control and experimental. In the control groups the effects on the liver of all of the elements in the experimental operations were studied by the performance of each operation separately in different animals. The results of the control part of the study have proved extremely interesting in themselves and present certain evidence throwing light on the general subject of infections of the upper part of the abdomen.

#### CONTROL STUDIES

The several control procedures, with the results obtained, were as follows:

*Ligation and Division of the Common Bile Duct.*—The abdomen was entered through a high midline incision. The common bile duct was dissected free and ligated in three places with no. 1 chromic catgut, about 1 cm. proximal to the point at which it enters the duodenum. Care was taken that the ligatures were below the entrance of the left hepatic duct. The duct was then divided between the two distal ligatures so that the proximal stump would be doubly ligated. The abdomen was closed in layers.

Three dogs were used. The animals showed clinical evidence of jaundice and died from the tenth to the thirteenth day after operation from bile peritonitis, resulting from rupture of the common bile duct or of the gallbladder. In dog 60 exploration was made on the thirteenth postoperative day, and a distended, grayish gallbladder containing 125 cc. of dark green, viscid bile was found. The liver in each animal was enlarged and deeply bile-stained. Microscopically, the liver showed jaundice with marked acute hepatitis and degeneration of the hepatic cells.

*Simple Cholecystogastrostomy.*—The abdomen was opened by means of a high midline incision. The gallbladder was aspirated of its bile, of which a culture was made. The gastrohepatic ligament was ligated and divided carefully so as to allow the stomach to be pulled up. The gallbladder was anastomosed to the stomach in the distal third region, from 3 to 4 cm. above the pyloric ring near the lesser curvature. The suture method of anastomosis was employed, two rows of no. 00 chromic catgut or, in a few instances, fine silk being used. No clamps were used. An attempt was made to have a resultant stoma of from 1

to 2 cm. in diameter. A small section of liver was removed for culture, and a microscopic examination was made whenever a cholecystogastrostomy was performed. The abdomen was then closed.

Three dogs were used. Exploration was made at various periods after operation, from the eighty-sixth to the one hundred and eighty-ninth day. In each animal the liver and gallbladder revealed gross pathologic changes. The stoma was patent, and the common duct was somewhat dilated. No particles of food were found in the gallbladder. Microscopic examination of the liver showed a slight infiltration with round cells throughout, with some fibrosis about the portal system and central veins.

*Combination of Cholecystogastrostomy and Ligation and Division of the Common Duct.*—Cholecystogastrostomy and ligation and division of the common duct were performed on three dogs after the technic described earlier. Exploration was made on the twelfth and the two hundred and eighth day after operation. On each animal the gallbladder was gray and somewhat dilated, as was the common duct. The stoma was patent. The liver macroscopically showed signs of fibrosis. Microscopic study of the liver revealed marked acute hepatitis, acute and chronic cholangitis and slight portal cirrhosis. These findings simply repeat the observations of Gatewood and Poppens,<sup>12</sup> Lehman,<sup>13</sup> Horsley<sup>14</sup> and others. They represent experimental results on which the idea of the importance of hepatic infections following cholecystogastrostomy has been founded.

*Gastric Division with a Polya-Balfour Anastomosis.*—The abdomen was opened by means of a high midline incision. The gastric vessels and the greater and lesser omentum were ligated and divided in the region of the distal third of the stomach. The stomach was then cut across between rubber-covered clamps. The distal third of the stomach was closed with two rows of no. 00 chromic catgut. The proximal portion of the stomach was anastomosed to the jejunum from 10 to 15 cm. from the duodenum, the Polya-Balfour technic being used. Two rows of no. 00 chromic catgut or fine silk were used. The abdomen was then closed (fig. 1 B).

Twenty-five dogs were used. Exploration was made between the fourteenth and the ninety-fourth day after operation. In each animal the gallbladder appeared to be normal, and an average of 33 cc. of bile was aspirated. Cultures of the bile showed *Staphylococcus albus* or *Bacillus coli-communis*. Negative cultures were obtained in 40 per cent. The liver appeared to be normal. Cultures of the liver revealed no organisms in 45 per cent of the dogs. The organism in the remaining cultures were *Staph. albus*, *B. coli* and, in one instance, *Streptococcus haemolyticus*. In cultures from the lumen of the closed distal stump *Staph. albus* and *Staphylococcus aureus* were most frequently found. *B. coli-communis* was also frequently recovered, as was *Bacillus*

aerogenes. Two cultures revealed bacilli of the *Salmonella* group, and two revealed no organisms. Microscopic examination of the liver showed in every instance a slight to marked infiltration with round cells and polymorphonuclears and fibrosis (figs. 2 and 3). These changes were most marked in the region of the central veins and portal system. In almost every liver there was fatty degeneration of the parenchyma, and the hepatic lobules were not distinct.

*Cholecystostomy.*—The abdomen was entered through a high mid-line incision. The gallbladder was exposed, and the bile was aspirated.

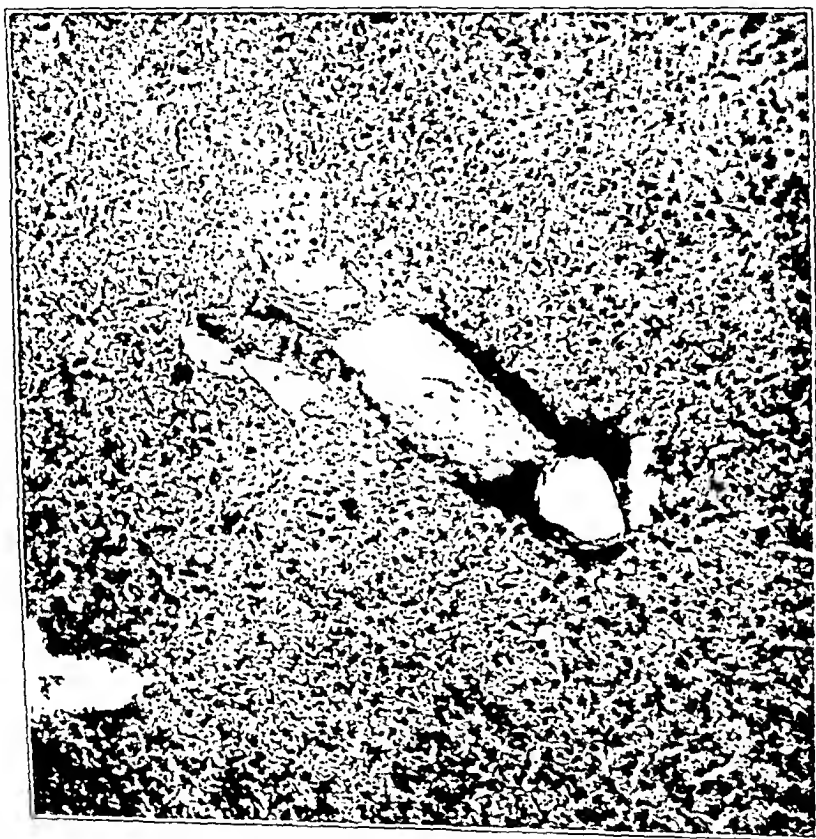


Fig. 2.—Low power photomicrograph of a section of the liver removed from dog 33 three months following gastric division and gastrojejunostomy (fig. 1 B). Note the cellular infiltration and the increase in the fibrous tissue.

The fundus of the gallbladder was then grasped, and an opening large enough to admit a small rubber tube was made. A purse-string suture was put in around the tubing, which was transfixed by the suture. The purse-string suture was drawn tight as the tubing was pushed in. A second row of no. 00 chromic catgut was then placed. The gallbladder was anchored to the peritoneum by two interrupted catgut sutures. The tube was brought to the outside, and the abdomen was closed.



Two dogs were used. The animals seemed to go down-hill fast, losing weight rapidly and showing a decrease in appetite. The bile decreased in flow until on the seventeenth postoperative day there was little greenish-yellow bile flowing from the cholecystostomy tube. Exploration revealed that the gallbladder was very much shrunk and surrounded by grayish fibrous tissue. The liver showed gross pathologic change, especially in the region closest to the gallbladder. Microscopic sections of the liver revealed acute hepatitis with fatty degeneration of



Fig. 3.—High power photomicrograph of the section shown in fig. 2.

the parenchyma. The infiltration with polymorphonuclears and round cells was most marked in the vicinity of the portal systems.

*Cholecystogastrostomy—Modified Technic.*—This method was an unsuccessful attempt to perform cholecystogastrostomy on the principle of the ureteral transplantation recently reported by Coffey.<sup>60</sup> It has no direct bearing on the experiments to follow.

60. Coffey, R. C.: Production of Aseptic Uretero-Enterostomy by Suture Transfixing Ureteral Wall and Intestinal Mucosa, J. A. M. A. **94**:1748 (May 31) 1930.

The abdomen was opened through a high midline incision. The gastrohepatic ligament was ligated and divided, and the stomach brought forward. An incision of about 3 inches (7.6 cm.) in length, which cut through the serosal and muscular coats, was made in the distal anterior third of the stomach. The gallbladder was pulled downward by means of a suture transfixing the serosal layer in the region of the fundus. The gallbladder was anchored to the stomach by means of this suture. A silk suture was taken between the stomach and the gallbladder, penetrating into the lumen of each. This suture was tied tight. The gallbladder was embedded in the wall of the stomach by suturing the muscular and serosal layers over it. The common bile duct was then dissected free and ligated as previously described. The abdomen was closed.

Four dogs were used. Exploration was made on from the seventeenth to the twenty-sixth day after operation. In no instance when the stomach was opened, was a stoma observed between the gallbladder and the stomach. The gallbladders of these dogs were markedly distended; they were dark green but free from adhesions. Macroscopically and microscopically, the livers revealed the pathologic pictures seen in cases of simple ligation and division of the common duct. One interesting fact was noted. In each dog the portion of the gallbladder embedded in the wall of the stomach had shrunk until it resembled a tube. The gastric mucosa over this region was slightly thickened.

In general, the results of the control procedures bring out the fact that all of the operations performed resulted in inflammatory changes in the liver. The changes followed not only the operations on the biliary tract but those limited to the stomach and the jejunum. The presence of this hepatitis will be further emphasized in the discussion of the results of the experimental procedures.

In addition, the occurrence of hepatitis following an operation on the stomach presents striking experimental evidence confirming the intimate pathologic association of the liver with the digestive tract. Graham<sup>61</sup> found similar hepatitis in three cases of appendicitis; its occurrence with cholecystitis is universal. Although again one must be cautious in comparing the dog with the human being, there arises the question as to whether inflammatory disease of the stomach and operations on the stomach in the human being may not result as constantly in hepatitis as cholecystitis has been shown to. A series of biopsies made on specimens of liver following gastric resection for noninflammatory disease of the stomach such as carcinoma would be interesting. This would be difficult to obtain because of the rarity of secondary

<sup>61</sup> Graham, E. A.: Diseases of the Gall Bladder and Bile Ducts, Philadelphia, Lea & Febiger, 1928, p. 122.

# Observations on Twenty-Five Animals on Which Cholecystogastrostomy and Ligation and Division of the Common Duct Were Performed

Dog	Date of Polya- Balfour Operation	Interval to Interval Explor- to Chole- cysto- gastro- stomy, Days	Interval to Chole- cysto- gastro- stomy, Days	Cultures				Microscopopathologic Changes in Liver	Date and Cause of Death	
				Second Operation		Third Oper- ation: Liver	Post-Mortem			
				Stump of Stomach	Bile					Liver
				Salmonella group	Negative					
19	7/30/30	98	9*							
28	10/17/30	32	92	Staph. aureus	Negative	Negative			11/13/30: Rile perito- nitis; rupture of gallbladder	
30	8/11/30	87	95	Staph. albus	Staph. albus	Negative			1/23/31: Acute dilata- tion of stomach	
33	8/12/30	94	94	B. coli	Hay bacillus	Negative			2/10/31: Perforated jejunal ulcer; peritonitis	
38	10/28/30	21	92	B. coli; Staph. albus	Negative	Staph. albus			10/11/31: Acute pan- creatitis	
40	11/20/30	20	71	Negative	Staph. albus	Staph. albus			9/8/31: Acute inflamtion	
41	11/25/30	15	90	B. coli; Staph. albus	Staph. albus	Staph. albus			2/19/31: Intestinal obstruction; intussusception	
						B. coli			3/11/31: Anesthesia	

43	10/28/30	23	32*	B. coli; Salmonella group	Negative	Staph. albus	.....	Slight infiltration with round cells and polymorpho-nuclears; fibrosis; cloudy swelling	.....	Slight infiltration with round cells and polymorpho-nuclears; fibrosis; cloudy swelling	12/22/30: Perforated jejunal ulcer; peritonitis
46	1/ 6/31	23	19*	Negative	Negative	Negative	B. coli	Slight infiltration with round cells and polymorpho-nuclears; fibrosis	.....	Slight infiltration with round cells and polymorpho-nuclears	2/17/31: Perforated jejunal ulcer; peritonitis
47	10/31/30	14	91	B. coli	Staph. albus	Staph. albus	Str. non-haemolyticus	Slight infiltration with round cells	Slight infiltration with round cells	Infiltration with round cells and polymorpho-nuclears; cloudy swelling	9/25/31: Autopsy revealed no cause of death
49	11/13/30	25	85*	B. coli; Staph. albus	Staph. albus	Staph. albus	Negative	Slight infiltration with round cells and polymorpho-nuclears; fibrosis; fatty degeneration	.....	Pathologic picture obscured by post-mortem change	3/3/31: Perforated jejunal ulcer; peritonitis
51	1/ 6/31	23	48	Staph. albus	Staph. albus	Staph. albus	Str. non-haemolyticus	Infiltration with round cells; fibrosis	Slight infiltration with round cells; fibrosis	Infiltration with round cells and polymorpho-nuclears; fibrosis; cloudy swelling	1/19/32: Acute haemilia
56	1/ 8/31	22	3*	B. coli	B. coli; Staph. albus	B. coli; Staph. albus	Negative	Slight infiltration with round cells and polymorpho-nuclears; fibrosis; fatty degeneration	.....	Slight infiltration with round cells; fibrosis; fatty degeneration	2/2/31: Intestinal obstruction due to adhesions
67	1/13/31	21	21*	Negative	Negative	Negative	B. coli	Slight infiltration with round cells; fibrosis; fatty degeneration; cloudy swelling	.....	Slight infiltration with round cells; fibrosis; fatty degeneration	2/21/31: Intestinal obstruction due to adhesions
63	1/14/31	23	13*	B. coli	B. coli	B. coli	B. coli	Infiltration with round cells and polymorpho-nuclears; fibrosis	.....	Pathologic picture obscured by post-mortem change	2/19/31: Bile peritonitis
61	1/14/31	23	40	B. coli; Staph. albus	Negative	Negative	Staph. albus	Infiltration with round cells and polymorpho-nuclears; fibrosis	Slight infiltration with round cells and polymorpho-nuclears	Infiltration with round cells and polymorpho-nuclears; cloudy swelling	6/13/31: Intestinal obstruction; intussusception
65	1/16/31	21	0*	Staph. albus	Negative	Negative	.....	Infiltration with round cells	.....	Infiltration with round cells	2/9/31: Anesthesia

*Observations on Twenty-Five Animals on Which Cholecystogastrotomy and Ligation and Division of the Common Duct Were Performed—Continued*

Dog	Date of Polya- Balfour Operation	Interval to Explor- ation to Chole- cysto- gastro- tomy, Days	Interval to Chole- cysto- gastro- tomy or Death, Days	Cultures			Microscopopathologic Changes in Liver	Post Mortem	Date and Cause of Death
				Second Operation					
				Stump of Stomach	Bile	Liver			
171	9/ 4/33	35	2*	Staph. albus	B. coli	Anaerobic bacillus; Staph. albus*	Amorobic bacillus	Slight infiltration with round cells and polymorpho- nuclears; fibrosis	10 11 33: Acute inflammation
172	9/ 4/33	35	93	Str. non- haemolyti- cus; B. coli	B. coli	B. coli; Str. non- haemolyticus; anaerobic bacillus	B. coli; B. aerogenes; anaerobic bacillus	Slight infiltration with round cells and polymorpho- nuclears; moder- ate fibrosis	1 17 33: Perforated jejunal ulcer; peritonitis
173	9/ 4/33	35	76	B. coli; hay bacillus	B. proteus	B. coli; hay bacillus	B. coli	Slight infiltration with round cells and polymorpho- nuclears	12 25 33: Acute dilata- tion of stomach
174	9/ 4/33	35	93	B. coli; hay bacillus	B. coli; B. aerogenes	Negative	B. coli; B. aerogenes; B. proteus	Moderate infiltra- tion with round cells and polymor- phonuclears; mod- erate fibrosis	
176	9/ 4/33	35	33*	B. coli; hay bacillus	Negative	Staph. albus	B. aerogenes	Slight infiltration with round cells and polymorpho- nuclears; cloudy swelling	
181	10/ 9/33	38	48*	B. coli; B. aerogenes	Negative	Staph. albus; gram-nega- tive bacilli	Staph. albus; anaerobic bacillus	Marked infiltration with round cells and polymorpho- nuclears; cloudy swelling	11/11/33: Intestinal obstruction at ileocecal valve
182	10/ 9/33	38	4*	B. coli; B. proteus; B. aerogenes	Negative	Anaerobic bacillus; gram-nega- tive bacillus	B. aerogenes	Marked infiltration with round cells and polymorpho- nuclears; hemor- rhagic areas	1/4/34: Perforated jejunal ulcer; peritonitis
183	10/ 9/33	38	55	B. coli	Negative	Staph. albus; anaerobic bacillus	B. coli; B. aerogenes; anaerobic bacillus	Marked infiltration with round cells and polymorpho- nuclears; moder- ate fibrosis	11/20/33: Abscesses of liver; gallbladder filled with blood
								Slight infiltration with round cells and polymorpho- nuclears	

laparotomy under these circumstances. However, a series of biopsies on the liver in cases of peptic ulcer in which the gallbladder is normal would be easier to obtain and might throw light on this subject.

#### EXPERIMENTAL STUDIES

The results of bacteriologic study will be discussed in the following paragraphs.

*First Stage Operations.*—Twenty-five dogs were first subjected to gastric division with a Polya-Balfour anastomosis. These were the animals studied in the control group before the second stage procedure.

*Second Stage Operations.*—At varying intervals of from fourteen to ninety-four days (table) a cholecystogastrostomy, the closed distal stump of the stomach being employed, with ligation and division of the common duct was performed on each animal (fig. 1 C). It was hoped by these means to unite the lumen of the gallbladder with the lumen of the stomach after the latter had had time to free itself from bacteria. At this operation a biopsy specimen of the liver was obtained, and cultures were taken from the liver tissue, the bile and the mucosa of the closed gastric stump, as detailed in the description of the primary procedure. As will be remembered, in all except two instances, the pouch was not free from bacteria, but the contamination was relatively slight as compared with the normal stomach of the dog, both as to the number and particularly as to the variety of the organisms (fig. 4). At the time of the second stage most of the dogs showed a gain in weight or maintained the weight recorded at the time of the first operation.

It was planned to complete the study of the experimental animals by a third operation, at which exploration was to be carried out and a specimen from the liver obtained to observe the changes in the liver about three months after the second stage.

Of the original twenty-five dogs, twelve died before this exploratory laparotomy (dogs 19, 43, 46, 49, 56, 57, 63, 65, 171, 176, 181 and 182). Dog 65 died apparently of the anesthetic at the time of the second stage operation. Dogs 43, 46, 49 and 181 died of perforated jejunal ulcers thirty-two, nineteen, eighty-five and forty-eight days, respectively, following cholecystogastrostomy. Dog 63 died of bile peritonitis. Dog 171 died of acute inanition (no other cause of death was found). Dog 19 died nine days after cholecystogastrostomy of bile peritonitis due to rupture of the gallbladder. Dogs 56 and 57 died of intestinal obstruction resulting from adhesions three and twenty-one days, respectively, following cholecystogastrostomy. Dog 182 was the only one to die of hepatic infection. There were eleven deaths occurring at exploratory laparotomy. Dogs 30 and 172 died of perforated jejunal ulcers. Dogs 40 and 64 died of intussusception. Dogs 173 and 28 died of acute dilatation of the stomach. Dog 33 died of acute pancreatitis. Dogs 38

and 51 died of acute inanition. Dog 41 died of the anesthetic on the day following the exploratory laparotomy. At autopsy dog 47 revealed no obvious cause of death. Two dogs are still living.

*Third Stage Operation.*—Only thirteen dogs, therefore, were subjected to the third stage exploratory operation. A biopsy specimen of the liver was taken at intervals of from forty to ninety-five days following cholecystogastrostomy. In addition, the livers of dogs 43, 46 and



Fig. 4.—Photographs of plate cultures from the closed gastric pouch and functioning stomach of dog 33. Plates *B* are on Endo's medium; plates *A* are on blood agar. Plates 1 are from the closed pouch; plates 2 are from the functioning stomach. These plates demonstrate the absence of colon bacilli in the closed pouch and a relatively slight contamination with staphylococci as compared to the functioning stomach.

181, which died of perforated jejunal ulcers, were obtained before post-mortem changes disturbed the pathologic picture, as were the livers of dog 19, which died of bile peritonitis, dogs 56, 57 and 176, which died of intestinal obstruction, dog 171, which died of acute inanition, dog

65, which died of the anesthetic, and dog 182, which died of abscess of the liver. Thus a total of twenty-three dogs were available for study of the effects on the liver of the experimental procedure.

At the exploratory operations there were found remarkably few adhesions and no marked gross pathologic changes in the gallbladder and liver (fig. 5). The absence of gross cholecystitis was a uniformly striking finding in comparison with the marked cholecystitis found after the usual type of experimental cholecystogastrostomy. Microscopic studies of the livers revealed in most instances a slight infiltration with polymorphonuclears and round cells and slight fibrosis, especially about

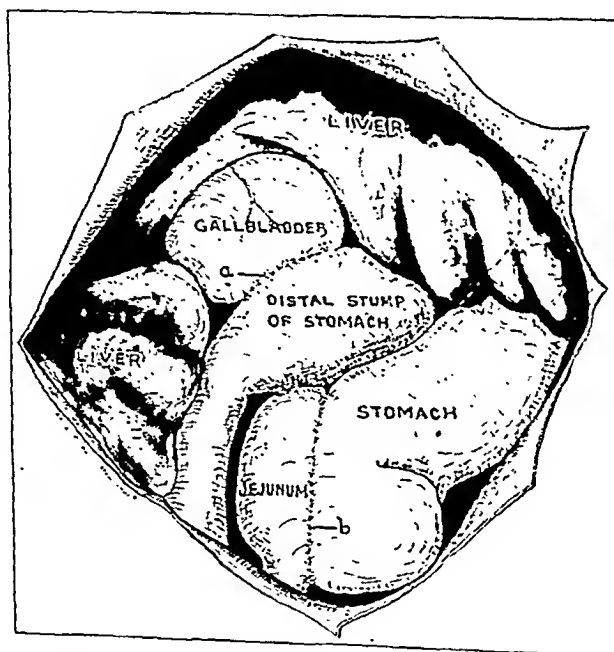


Fig. 5.—Drawing of the liver and the anastomosis as seen at exploratory operation three months after the second stage operation; *A*, cholecystogastrostomy, and *B*, gastrojejunostomy.

the portal system and central veins (figs. 6 and 7). The hepatic lobules were not distinct, and there was an absence of fatty degeneration. These changes seemed to be slightly more marked in the sections from the right lobes of the liver than in those from the left lobes. These sections, when compared with sections from the same livers removed at intervals following the first stage Polya-Balfour anastomosis, showed no more—perhaps less—infiltration and fibrosis. This comparison must be strongly emphasized. A section of liver from dog 182 was the only one to show a frank hepatic infection with formation of abscesses. Cultures of the livers revealed *B. coli-communis*, *Staph.*



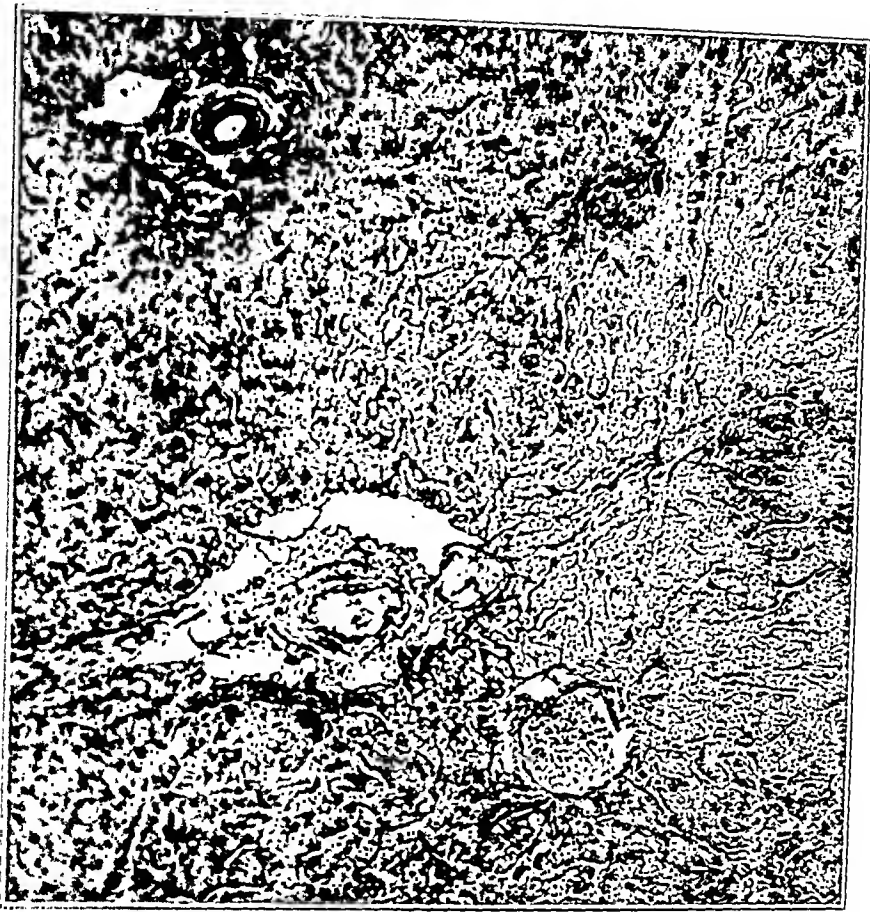


Fig. 6.—Low power photomicrograph of a section of the liver removed three months following the second stage operation. Compare with figure 2. No increase in the hepatitis is seen.

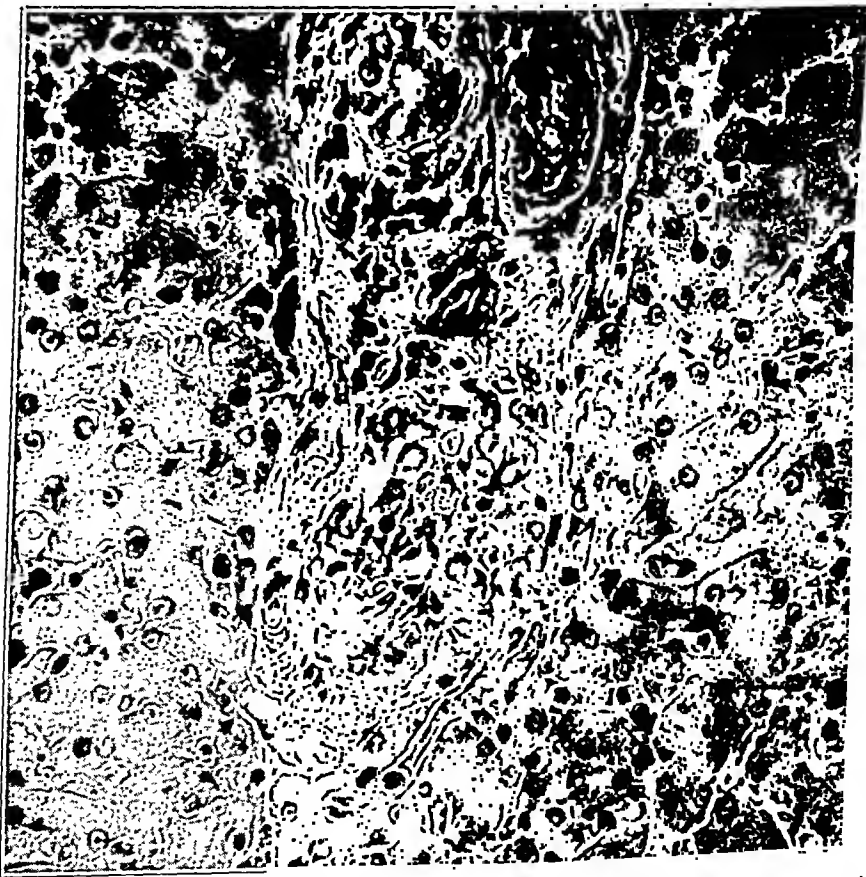


Fig. 7.—High power photomicrograph of the section of the liver shown in figure 6. Compare with figure 3.



Fig. 8.—Photograph of the stomach of a dog which died of perforation of a gastrojejunal ulcer. The site and appearance are entirely characteristic.

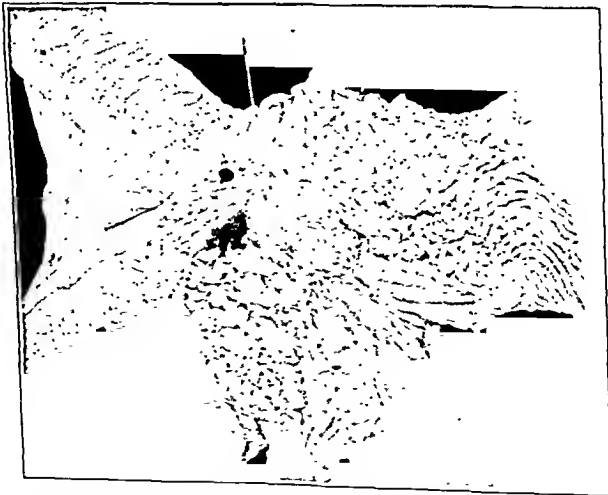


Fig. 9.—Photograph of the ulcer shown in figure 8, viewed from the lumen.

albus, *Streptococcus nonhaemolyticus* and *Bacillus Welchii*. Twenty-five per cent of the cultures revealed no organisms.

It is interesting that dogs 43 and 46, which died of peritonitis resulting from a ruptured ulcer before the exploratory operation, showed no more marked hepatitis than that found in the thirteen dogs from which specimens of liver were obtained at operation. On the other hand, the sections of liver obtained from dog 30 following death from perforation of a jejunal ulcer showed a much more acute picture of hepatitis than did sections of the same liver removed at operation ninety-five days previously. Furthermore, the livers of dog 19 (peritonitis) and dogs 56, 57 and 176 (obstruction), also obtained post mortem before exploratory laparotomy, showed no increase in hepatitis over that shown at the time of operation, respectively nine, three, twenty-one and thirty-three days previously.

The pathologic characteristics of the jejunal ulcers, from the perforation of which six animals died, is entirely similar to that of the so-called gastrojejunal ulcer found in man following gastrojejunostomy. The ulcers varied in number from one to four. They were invariably located in the jejunum opposite the open end of the stomach, toward which the food current is projected by gastric peristalsis (figs. 8 and 9).

#### COMMENT

At the initiation of this study it was assumed that the blind pouch of the dog's stomach would become relatively free from organisms and that an anastomosis with the gallbladder in this location would therefore more nearly simulate the conditions found in man. As has been shown earlier, the pouch still contains a considerable number of organisms even three months after isolation, although the number was fewer than that obtained in the normal dog's stomach. The truth of this assumption was tested by comparative cultures from the stomach and the closed pouch of the same animal (fig. 4). The importance of this deviation from the expected results becomes small in view of the other findings reported. It is also to be noted that bacteria were often recovered from the hepatic tissue and the bile in dogs that were apparently normal and on which no operation had been performed.

The striking fact is that thirteen dogs on which an exploratory operation was performed from one to three months after cholecystogastrostomy under the given conditions and ten dogs dying at shorter intervals after the same operation showed no increase of hepatic inflammation over that found at the time of a cholecystogastrostomy which followed an operation on the stomach. The degree of hepatitis found in three control animals in which simple cholecystogastrostomy with ligation and division of the common duct was performed according to

the usual experimental technic agrees materially with that reported by earlier experimenters. Of more importance is the fact that this degree of hepatitis is unmistakably greater than that found in the experimental animals. In other words, under one set of conditions, cholecystogastrostomy results in no augmentation of hepatitis already present, whereas under another set of conditions cholecystogastrostomy results in a marked development of hepatitis in a previously normal liver. These facts, of course, indicate clearly that the union of the gallbladder

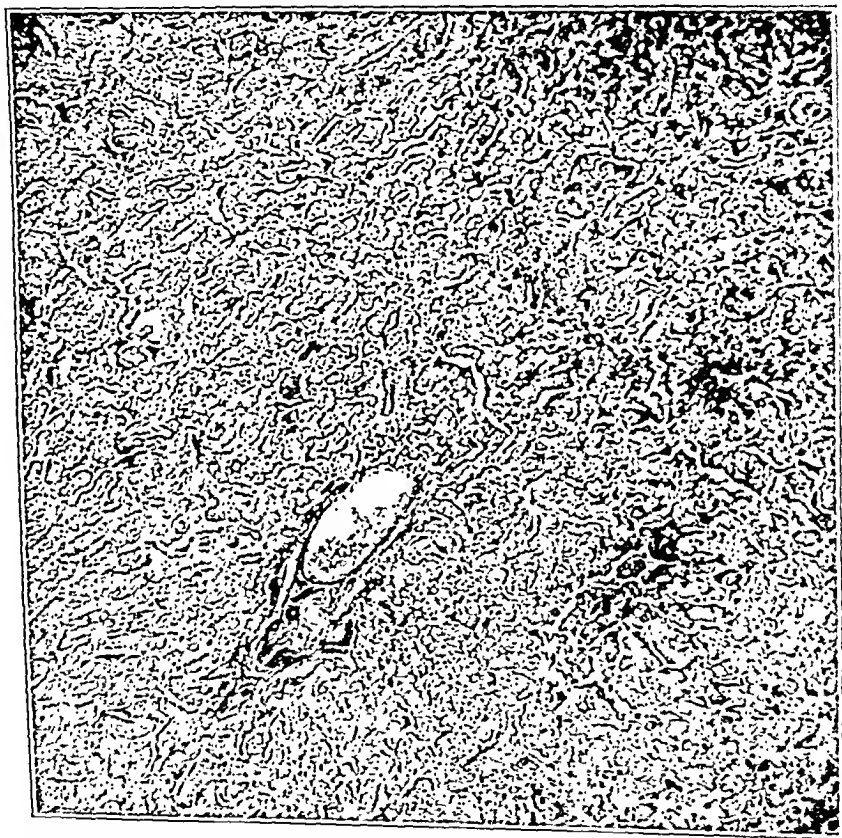


Fig. 10.—Low power photomicrograph of a section of the normal liver of a dog. Compare with figures 2 and 6.

to the stomach in experimental animals in itself does not entail marked hepatic infection. The conditions of the present experiment were planned to minimize the exposure of the gallbladder to contamination, and the pathologic results suggest that this has been accomplished no matter what the bacteriologic results are. These observations taken in conjunction with the paucity of recorded specific evidence of hepatic infection following cholecystogastrostomy in man suggest strongly that the fear of this sequel is unjustified. The results of the present

cholecystogastrostomy is the only plausible experimental evidence in support of the possibility of hepatic infection following cholecystogastrostomy.

In view of the fact that the observations are somewhat opposed to general acceptance of the value and to previous experimental work, it seems reasonable to doubt the general validity until this work has been repeated on other laboratory animals and with larger numbers of animals. The authors of the above suggestion and have collaborators on cholecystogastrostomy in progress and I mention it again here.

If there is a definite substantiated, it becomes obvious that there is no experimental support for the claim of operation for the purpose of short-circuiting the biliary system. The historical evidence seems to point to a decrease in the frequency of both cholecystenterostomy. As has been said, cholecystitis and infection have been found following cholecystogastrostomy as well as cholecystitis has been found following cholecystenterostomy. It is important that it must not be assumed from these statements that no cholecystitis has ever occurred. The only objection to cholecystogastrostomy is that it is not a cure.

It is to be noted that the jejunal perforations of jejunal ulcers in this series occurred after the second stage. The exposure of the jejunum to the contents of gastric contents originated at the time of the Polya-Bellomy operation, that stage. It is hard to imagine how the delivery of bile into the duodenum through the pylorus following cholecystogastrostomy can be physiologically different from the delivery of bile through the papilla of Vater previous to that operation, so far as the clinical protection of the jejunal mucosa is concerned. In other words, it is unlikely that the cholecystogastrostomy itself has anything to do with the occurrence of the ulcers, in spite of this time relationship.

The quantitative relationships of the bacteria found in the closed stump of the stomach have been mentioned, and the relationship of these findings to the general experimental problem has been discussed. A word or two may be said about the qualitative bacterial findings. From a study of cultures taken from the liver and bile there was found no relationship between the type of organism and the degree or character of the hepatitis. No organisms were recovered from three livers that showed definite hepatitis, and organisms were on several occasions recovered from a liver that showed no hepatitis.

#### CONCLUSIONS

A study of the literature of cholecystogastrostomy has shown a fear of hepatic infection as a sequel to the operation, without confirmatory evidence in the form of clinical, operative or postmortem reports of cases.

The results of previous experimental attacks on the problem confirm this fear. These, however, are subject to serious criticism in their application to the human being.

By creating a gastric pouch separated from the current of food, cholecystogastrostomy can be performed on the dog under conditions more nearly comparable bacteriologically with those under which the operation is performed in the human being.

In twenty-five dogs the performance of the preliminary operation on the stomach resulted in hepatitis. This pathologic change is less in degree than that resulting from the ordinary experimental performance of cholecystogastrostomy.

In twenty-two dogs on which cholecystogastrostomy was performed in a gastric pouch closed at the upper end the hepatitis found at various periods after the second stage operation was no greater in degree than that found following the preliminary operation.

The evidence presented, therefore, tends to discredit the common opinion among surgeons that hepatic infection is a dangerous sequel to cholecystogastrostomy.

series of experiments removes the only plausible experimental evidence supporting the sequence of hepatic infection following cholecystogastrostomy.

In view of the fact that these conclusions are somewhat opposed to general surgical thought and to previous experimental work, it seems wise to reserve a final opinion as to their validity until this work has been repeated in other laboratories and with larger numbers of animals. The work of Weinberg<sup>15</sup> and his collaborators on cholecystogastrostomy in a monkey may be mentioned again here.

If these results are substantiated, it becomes obvious that there is no need to devise any other clinical operation for the purpose of short-circuiting the biliary system. The historical evidence seems to point to this operation in preference to cholecystenterostomy. As has been said, no reports of infection have been found following cholecystogastrostomy, whereas several have been found following cholecystenterostomy. Let me repeat that it is not wise to assume from these statements that no such instances have occurred. The only objection to cholecystogastrostomy so far advanced is removed.

It is to be noted that the six perforations of jejunal ulcers in this series occurred after the second stage. The exposure of the jejunum to unmodified gastric contents originated at the time of the Polya-Balfour anastomosis (first stage). It is hard to imagine how the delivery of bile into the duodenum through the pylorus following cholecystogastrostomy can be physiologically different from the delivery of bile through the ampulla of Vater previous to that operation, so far as the chemical protection of the jejunal mucosa is concerned. In other words, it is unlikely that the cholecystogastrostomy itself has anything to do with the occurrence of the ulcers, in spite of this time relationship.

The quantitative relationships of the bacteria found in the blood stump of the stomach have been mentioned, and the relationship of these findings to the general experimental problem has been discussed. A word or two may be said about the qualitative bacterial findings. From a study of cultures taken from the liver and bile there was found no relationship between the type of organism and the degree or character of the hepatitis. No organisms were recovered from three livers that showed definite hepatitis, and organisms were on several occasions recovered from a liver that showed no hepatitis.

#### CONCLUSIONS

A study of the literature of cholecystogastrostomy has shown that the sequence of hepatic infection as a sequel to the operation, without convincing evidence in the form of clinical, operative or post-mortem findings in cases.

The results of previous experimental attacks on the problem confirm this fear. These, however, are subject to serious criticism in their application to the human being.

By creating a gastric pouch separated from the current of food, cholecystogastrostomy can be performed on the dog under conditions more nearly comparable bacteriologically with those under which the operation is performed in the human being.

In twenty-five dogs the performance of the preliminary operation on the stomach resulted in hepatitis. This pathologic change is less in degree than that resulting from the ordinary experimental performance of cholecystogastrostomy.

In twenty-two dogs on which cholecystogastrostomy was performed in a gastric pouch closed at the upper end the hepatitis found at various periods after the second stage operation was no greater in degree than that found following the preliminary operation.

The evidence presented, therefore, tends to discredit the common opinion among surgeons that hepatic infection is a dangerous sequel to cholecystogastrostomy.



# EXPERIMENTAL STUDIES ON PULMONARY SUPPURATION

J. J. LONGACRE, M.D.

AND

LOUIS G. HERRMANN, M.D.

CINCINNATI

In 1819 Laennec<sup>1</sup> published the first authentic report of a case of pulmonary gangrene. Subsequently, cases were noted by Leyden and Jaffe<sup>2</sup> (1866), who first noted the presence of spirochetes and other bacteria in the sputum and gangrenous tissue of patients suffering from this disease. The work of Rona<sup>3</sup> (1905) and especially that of Castellani<sup>4</sup> in 1906 attracted the attention of the medical profession to the possible etiologic relationship of the spirochetes to bronchopulmonary lesions. For the next decade heated controversies were waged, especially in France, with regard to the rôle played by the various anaerobes in pulmonary suppuration. A voluminous literature was evolved, filled with hypotheses but surprisingly lacking in experimental and clinical data.

## CONCEPTS OF ETIOLOGY IN THE LITERATURE

In 1919 Heuer and Holman<sup>5</sup> made the first attempt to produce a pulmonary abscess by placing infected bullets in pulmonary tissue. Following numerous attempts one small abscess was produced. Aschner<sup>6</sup> in 1922 referred to numerous unsuccessful attempts to produce an abscess of the lung by the introduction of infected material into the bronchial tree. Fetterolf and Fox<sup>7</sup> in 1923 were the first

---

From the Department of Surgery of the College of Medicine of the University of Cincinnati and of the Cincinnati General Hospital.

1. Laennec, T. A.: *Traité du diagnostic des poudrons et du cœur*, Paris, L. A. Brosseau, 1819, vol. 2.

2. Leyden, E., and Jaffe, M.: *Ueber putrid Sputa, nebst einigen Bemerkungen über Lungenbrand und putrid bronchitis*, *Deutsches Arch. f. klin. Med.* **2**:488, 1867.

3. Rona, S.: *Zur Aetiologie und Pathogenese der Angina, der Stomatitis gangraenosa, des Noma und der Lungengangrän*, *Arch. f. Dermat. u. Syph.* **74**: 171, 1905.

4. Castellani, A.: *Note on a Peculiar Form of Hemoptysis with the Presence of Numerous Spirochaetae in the Expectoration*, *Lancet* **1**:1384, 1906.

5. Heuer, G., and Holman, E., cited by Holman: *Experimental Studies in Pulmonary Suppuration*, *Surg., Gynec. & Obst.* **44**:328, 1927.

6. Aschner, P. W.: *The Pathology of Lung Suppuration*, *Ann. Surg.* **75**: 321, 1922.

7. Fetterolf, G., and Fox, H.: *The Reaction of Peritonsillar Tissues to Tonsillectomy*, *Am. J. M. Sc.* **166**:802, 1923.

to suggest the possible etiologic relationship of septic emboli when they succeeded in producing definite pulmonary abscesses by the injection of bits of tonsillar tissue into the jugular vein. In the same year Kline and Blankenhorn<sup>8</sup> produced pleuropulmonary gangrene in one rabbit by the intrabronchial injection of material from a carious tooth. Lambert and Miller<sup>9</sup> in 1924 injected a mixed culture of pure anaerobes intravenously into rabbits and after many failures produced one abscess of the lung, which occurred subsequent to the development of suppurative thrombophlebitis at the point of the injection. In 1925 Ribierre and Kermorgant<sup>10</sup> reported the production of hemorrhagic bronchitis by the intrabronchial injection of a culture of spirochetes. In 1926 Cutler and Schleuter<sup>11</sup> produced acute pulmonary abscess regularly by the introduction of emboli containing various aerobic organisms. Their later studies<sup>12</sup> showed that the virulence of the organisms and the resistance of the host were of great importance. Holman, Chandler and Cooley<sup>13</sup> demonstrated that tuberculous emboli introduced into the jugular vein initiated the pathologic changes in the pulmonary tissue resulting successively in anemia, infarction, caseation, central softening and the formation of an abscess. In 1927 C. E. Smith and Rusk<sup>14</sup> and D. T. Smith<sup>15</sup> reported the production of all types of acute and chronic fusospirochetal disease in the lungs of mice, guinea-pigs and rabbits by the intratracheal injection of sputum and scrapings from the crypts of pyorrhea alveolaris. About the same time Ghiron and Maddalena<sup>16</sup> produced abscess by the introduction of a segment of vein containing gastric and intestinal contents into the jugular vein. Crowe and Scarff<sup>17</sup>

8. Kline, B. S., and Blankenhorn, M. A.: Spirochaetal Pulmonary Gangrene, *J. A. M. A.* **81**:719 (Sept. 1) 1923.

9. Lambert, A. V. S., and Miller, J. A.: Abscess of the Lung, *Arch. Surg.* **8**:446 (Jan.) 1924.

10. Ribierre, P., and Kermorgant, Y.: Pulmonary Spirochaetosis, *Compt. rend. Soc. de biol.* **93**:1351, 1925.

11. Cutler, E. C., and Schleuter, S. A.: The Experimental Production of Abscess of the Lung, *Ann. Surg.* **84**:256, 1926.

12. Cutler, E. C.; Halloway, J. W., and Schleuter, S. A.: Reaction of Immunity Through Experimental Production of Abscess of the Lung, *Ann. Surg.* **86**:165, 1927.

13. Holman, E.; Chandler, L. R., and Cooley, C. L.: Experimental Studies in Pulmonary Suppuration, *Surg., Gynec. & Obst.* **44**:328, 1927.

14. Smith, C. E., and Rusk, G. T.: Pulmonary Spirochaetosis, *Am. J. Path.* **3**:225, 1927.

15. Smith, D. T.: Experimental Aspiratory Abscess, *Arch. Surg.* **14**:231 (Jan.) 1927.

16. Ghiron, V., and Maddalena, P.: Sulla produzione sperimentale di polmonite e gangrene polmonari, *Bull. atti. d. v. Accad. med. di Roma* **53**:302, 1927.

17. Crowe, S. J., and Scarff, J. E.: Experimental Abscess of the Lung in the Dog, *Arch. Surg.* **16**:176 (Jan.) 1928.

in 1928 reported the production of abscess of the lung in eight dogs by the implantation in the bronchus of a pledget of cotton soaked in pyorrheal scrapings. They also reported the occurrence of abscess subsequent to the production of a foul sinusitis caused by the introduction of pyorrheal scrapings into the frontal sinus. In the same year Allen<sup>18</sup> reported the production of multiple abscesses in 100 per cent of his animals following the intrabronchial inoculation of warm sputum, provided the bronchus was ligated immediately following the injection. In 1928 Herrmann, Cutler and Weidlein<sup>19</sup> modified the original Cutler-Schleuter method and produced chronic abscess of the lung by an embolus impregnated with pyorrheal exudate. David T. Smith at this time reported being unable to produce suppuration of the lung by the intrabronchial injection of pure cultures of the anaerobes into guinea-pigs. In 1929 Lambert and Weeks<sup>20</sup> noted that when washed sputum containing both aerobes and anaerobes was used the abscess produced contained only anaerobes, the aerobes having disappeared.

The bacteriologic study of numerous clinical abscesses of the lung has revealed a bacterial flora similar to that of an unhygienic buccal cavity. The strongest argument for the theory of aspiration is the close similarity of the organisms of pulmonary suppuration to those found in the upper respiratory tract. Daily and Daily<sup>21</sup> reported the aspiration of blood in 78 per cent of one hundred patients during tonsillectomy while under general anesthesia. Iglauer<sup>22</sup> found blood in the trachea in 30 per cent of his cases (fifty) after local anesthesia. Myerson<sup>23</sup> showed bacterial contamination in 76 per cent of a large series of patients who underwent tonsillectomy, even though the head was tilted back at an angle of 45 degrees. He drew the pertinent conclusion that bland substances, such as mucus, saliva and blood, do not stimulate the mucosa of the larynx and trachea sufficiently to excite cough. Only when the mass of aspirated material is sufficient to interfere with the passage of air or when the mucosa is hyperirritable and inflamed is the cough reflex called into play. This fact of frequent

18. Allen, D. S.: Etiology of Abscess of Lung, *Arch. Surg.* **16**:179 (Jan.) 1928.

19. Herrmann, L. G., and Cutler, E. C.: A Method for the Experimental Production of Chronic Abscess of the Lung, *Proc. Soc. Exper. Biol. & Med.* **26**:28 (Oct.) 1928. Weidlein, I. P., and Herrmann, L. G.: Abscess of the Lung: Experimental Studies in Chronicity, *J. A. M. A.* **91**:850 (Sept. 22) 1928.

20. Lambert, A. V. S., and Weeks, C.: Experimental Production of Abscess of Lung, *Arch. Surg.* **18**:446 (Jan.) 1929.

21. Daily, L., and Daily, R. K.: Bronchoscopic and Esophagosopic Operations in Tonsillectomies, *Texas State J. Med.* **23**:277 (Aug.) 1927.

22. Iglauer, S.: Post-Tonsillectomy Lung Abscess, *Ann. Otol., Rhin. & Laryng.* **37**:231, 1928.

23. Myerson, M. C.: Pulmonary Aspects of Tonsillectomy Under General Anesthesia, *Laryngoscope* **32**:929, 1922.

contamination of the lower portion of the respiratory tract is the strongest argument against the hypothesis of aspiration as the origin of abscess of the lung. Myerson reported an evacuation time of twelve minutes in the lower portion of the respiratory tract owing to ciliary action and bronchial peristalsis. Hedblom and his associates<sup>24</sup> suggested that in certain instances the mechanism of elimination fails and that fluid may gravitate out into the periphery beyond the field of the scavenging activity of cough and ciliary action. Archibald<sup>25</sup> found that when substances were aspirated beyond a certain zone in the bronchial tree cough had the effect of driving them farther toward the periphery.

In short, both clinical and laboratory experience has demonstrated the lung to be very susceptible to the formation of abscess from septic embolism and to be very resistant to bronchogenic inoculation. Certain types of abscess are purely embolic; others are purely bronchogenic, but a large group is not explained by either mode of origin. For these cases certain investigators (Holman and Mathes;<sup>26</sup> Van Allen, Adams and Hrdina<sup>27</sup>) suggested the combination of the embolic route and aspiration. Holman and Mathes reported hemorrhagic infarction in twenty-eight of thirty-two animals following the introduction of one sterile and one infected embolus. Van Allen and his associates, on the other hand, suggested that septic embolism produces the initial acute abscess which is secondarily invaded by intrabronchial contaminating organisms, which in turn exert a profound effect on the chronicity and the virulence of the preexisting abscess of the lung. This accounts in the embolic theory for the disparity between the existing bacterial flora of the abscess and that of the operative field. It also shows why the organisms normally resident in the upper portion of the respiratory tract are found in abscesses of the lung despite the difficulty of producing experimental bronchiogenic lesions.

#### EXPERIMENTAL STUDIES

To recapitulate: Pulmonary abscess may be pictured bacteriologically as originating from an uncertain agent but ending in a definite

24. Hedblom, C. A.: Pulmonary Abscess and Bronchiectasis, Etiology and Diagnosis, *Long Island M. J.* **92**:378, 1930. Hedblom, C. A.; Joannides, M., and Rosenthal, S.: Pulmonary Suppuration, *Ann. Surg.* **88**:823, 1928.

25. Archibald, E. W., and Brown, A. L.: Dangers of Introducing Iodized Oil into the Tracheo-Bronchial Tree, *J. A. M. A.* **88**:1310 (April 23) 1927.

26. Holman, E., and Mathes, M. E.: The Production of Intra-Pulmonary Suppuration by the Secondary Infection of a Sterile Embolic Area, *Arch. Surg.* **19**:1246 (Dec.) 1929.

27. Van Allen, C. M.; Adams, W. E., and Hrdina, L. A.: Embolism in Bronchiogenic Infection of the Lung, *Arch. Surg.* **19**:1279 (Dec.) 1929.

clinical picture that includes a terrific secondary invasion of organisms of various and diverse types. Several questions immediately present themselves:

1. What organisms or group of organisms is responsible for the original infection?

2. Does the study of bacterial invasion reveal anything with regard to the pathogenesis of pulmonary suppuration?

3. In what ways do the course and prognosis of these lesions depend on the organisms or group of organisms present?

The theories with regard to a specific initial infection rest on very uncertain data. The most logical assumption is that a number of

TABLE 1.—*Results of Experiments with Intrabronchial Implantation*

Ex- per- iment	Dog	Material Implanted*	Cause of Death	Duration of Roentgenographic Signs	Lesion Found at Autopsy
1	4	S. E., pyorrhea; Br.	Killed	No lesion	No pulmonary lesion
2	5	S. E., B. coli (virulent); Br.	Pneumonitis	Two days	Pneumonitis and empyema
3	7	S. E., B. coli (virulent); Br.	Killed	No lesion	No pulmonary lesion
4	6	S. E., pyorrhea; Br.	Killed	No lesion	Fibrosis about lead shot
5	312	S. E., pyorrhea; Br.	Killed	No lesion	No pulmonary lesion
6	313	S. E., pyorrhea; Br.	Killed	No lesion	No pulmonary lesion
7	314	S. E., pyorrhea; Br.	Killed	No lesion	No pulmonary lesion
8	26	S. E., pyorrhea; Br.	Distemper	No lesion	No pulmonary lesion
9	37	S. E., pyorrhea; Br.	Killed	No lesion	No pulmonary lesion
10	10	Pyorrhea; Br.	Killed	No lesion	No pulmonary lesion
11	316	Pyorrhea; Br.	Killed	No lesion	Early bronchiectasis
12	317	Pyorrhea; Br.	Killed	No lesion	No lesion
13	315	Pyorrhea; Br.	Killed	No lesion	Early bronchiectasis
14	11	Pyorrhea; implantation in frontal sinus	Killed	No lesion	No pulmonary lesion
15	57	Washings from antrum; Br.	Killed	No lesion	No pulmonary lesion
16	59	Washings from antrum; implantation into frontal sinus	Killed	No lesion	No pulmonary lesion
17	60	Washings from antrum; Br.	Killed	No lesion	No pulmonary lesion
18	56	Washings from antrum; Br.	Killed	No lesion	No pulmonary lesion

\* S. E. means sterile embolus; Br., bronchoscopic implantation.

organisms are involved, but not the same ones in each case. As a clinical abscess represents an advanced stage, with considerable secondary flora present, it is within the range of probability that the original infectious agent has relatively little, if any, clinical significance.

Cognizant of the scope of this problem, we laid out a detailed, controlled group of experiments. This paper represents the preliminary report. In the first place, a series of experiments was planned in order to contrast the mode of bacterial invasion with relation to the pathogenesis of the lesion.

The endobronchial approach was tried in eighteen dogs. Previous to bronchoscopic implantation of infectious material the cough reflex was abolished by the administration of  $\frac{1}{2}$  grain (0.03 Gm.) of morphine and the bronchial mucosa was cocaineized. Following the bronchoscopy performed with the dog under ether anesthesia, the animal was given

TABLE 2.—*Results of Experiments with Embolic Implantation of a Vein Segment in the Jugular Vein*

Experiment	Dog	Material	Duration of Lesion, Days	Cause of Death	Lesion at Autopsy
1	13	Pyorrhea	15	Pulmonary hemorrhage	Abscess of lungs
2	14	Pyorrhea	120	Convulsions; killed	Abscess of lung; cerebral embolism
3	15	Pyorrhea	20	Killed in fight	Abscess of lung
4	16	Pyorrhea	150	Cerebral embolism; convulsions	Abscess of lung
5	22	Pyorrhea	80	Killed	Abscess of lung (chronic)
6	33	Pyorrhea	6	Empyema	Empyema; abscess of lung
7	63	From abscess in dog 24	35	Killed in fight	Abscess of lung (chronic)
8	67	From abscess in dog 22	86	Killed	Abscess of lung (chronic)
9	105	From abscess in dog 39	90	Killed	Abscess of lung (small)
10	106	From abscess in dog 39	185	Killed	No demonstrable lesion
11	8	Pyorrhea	230	Killed	Epitheliated cavity (no activity)
12	12	Pyorrhea	155	Killed	Area of fibrosis (no activity)
13	193	Pyorrhea	36*	Killed	Abscess of lung
14	194	Pyorrhea	40*	Killed	Abscess of lung
15	208	Pyorrhea	26*	Killed	Abscess of lung
16	278	Pyorrhea	13	Toxemia	Abscess of lung
17	308	Pyorrhea	26*	Empyema	Abscess of lung
18	311	Pyorrhea	41*	Killed	Abscess of lung
19	256	From abscess in dog 193	30	Killed	Large abscess of lung

\* The involved lung was removed by pneumonectomy.

TABLE 3.—*Results of Experiments with Embolic Implantation of Blood Clot in the Jugular Vein*

Experiment	Dog	Material	Duration of Lesion, Days	Cause of Death	Lesion at Autopsy
1	17	Pyorrhea	20	Empyema	Abscess of lung; empyema
2	18	Pyorrhea	42	Empyema	Abscess of lung; empyema
3	19	Pyorrhea	65	Killed	No demonstrable lesion
4	20	Pyorrhea	58	Killed	Abscess of lung
5	23	Pyorrhea	4	Empyema; convulsions	Abscess of lung; empyema
6	24	Pyorrhea	47	Killed	Chronic abscess of lung
7	32	Pyorrhea	9	Empyema; pulmonary hemorrhage	Abscess of lung; empyema
8	35	Pyorrhea	23	Pulmonary hemorrhage	Abscess of lung
9	39	Pyorrhea	110	Killed	Chronic abscess of lung
10	40	Pyorrhea	158	Killed	Chronic abscess of lung
11	43	Pyorrhea	75	Empyema	Abscess of lung; empyema
12	44	Pyorrhea	34	Empyema	Abscess of lung; empyema
13	45	Pyorrhea	16	Empyema	Abscess of lung; empyema
14	47	From abscess in dog 24	7	Pulmonary hemorrhage	Abscess of lung; empyema
15	62	From abscess in dog 24	6	Pulmonary hemorrhage	Abscess of lung; empyema
16	49	From abscess in dog 24	45	Killed in fight	Abscess of lung; empyema
17	64	From abscess in dog 24	2	Distemper	Hemorrhagic pneumonitis
18	81	From abscess in dog 22	16	Killed in fight	Abscess of lung
19	84	From abscess in dog 22	8	Killed in fight	Abscess of lung
20	85	From abscess in dog 22	26	Found dead in cage	Abscess of lung
21	88	From abscess in dog 22	30	Distemper	Abscess of lung; distemper

$\frac{1}{4}$  grain (0.015 Gm.) of morphine. Cotton plugs impregnated with infectious material (such as scrapings from the gingival trenches of patients with pyorrhea alveolaris and washings from the antrum) were implanted in the secondary and tertiary bronchi of seven dogs by means of the bronchoscope. In nine animals the resistance of a certain portion of the pulmonary parenchyma was lowered previous to intra-bronchial implantation by the release of sterile emboli in the form of segments of veins into the jugular vein. In two other dogs the material was implanted in the frontal sinus. The animals were closely observed, but in no case did a pulmonary abscess develop (table 1). In two of the animals signs of early bronchial ulceration and dilatation (early



Fig. 1.—A chronic abscess of the lung produced by the embolic implantation of scrapings from crypts of pyorrhea alveolaris in vein segments, showing the zone of infiltration about the abscess and illustrating the rupture of the abscess into the bronchus. The specimens were obtained by pneumonectomy.

bronchiectasis) were noted at autopsy, beyond the point of occlusion of the bronchus by the cotton plug (fig. 2). The distal bronchus was filled with a mucopurulent secretion, but in no case was any area of localized pulmonary necrosis found, despite the fact that many of the animals were killed from forty-two to seventy days after the bronchoscopic implantation.

In another series of forty dogs the infectious material was introduced in the form of emboli (vein segment or blood clot). Herrmann's modification of the original Cutler-Schleuter technic being used. In most instances the infectious material was scrapings from the gingival trenches

of patients with protracted pyorrhea alveolaris. In some cases the material was derived from an abscess of the lung of a killed animal. This series was divided into two groups: (1) that in which the vein segments were used as emboli (table 2), and (2) the group in which blood clots were used (table 3). A parallel analysis of both groups disclosed interesting data, to be taken up later. In this series 92.5 per cent of the animals were found to have an abscess of the lung at

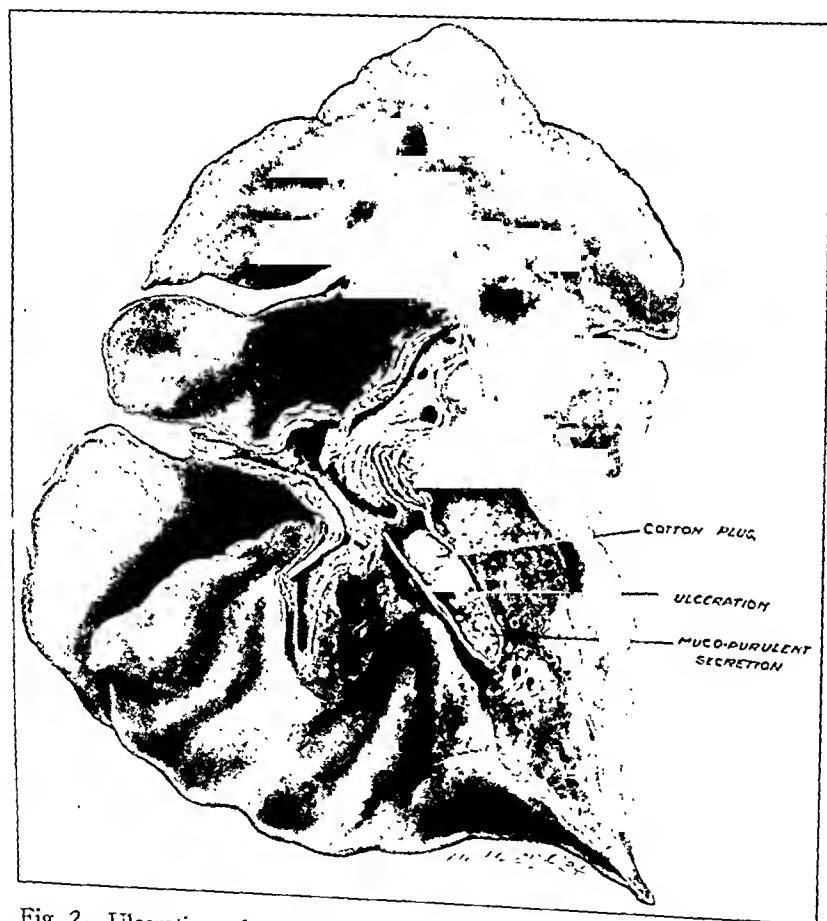


Fig. 2.—Ulceration of the bronchial mucosa such as was noted distal to the point of bronchial occlusion in several cases of endobronchial implantation. The specimen was obtained by pneumonectomy.

autopsy. One animal died of hemorrhagic pneumonitis. In only two animals were no lesions demonstrable at autopsy, and they were killed sixty-five and one hundred and eighty-five days, respectively, after the introduction of emboli. The abscesses formed varied from acute abscesses found in the animals dying in from four to nine days of empyema or pulmonary hemorrhage to chronic abscesses of from one



hundred and ten to one hundred and fifty days in duration. In an animal killed at the end of two hundred and thirty days an epitheliated cavity was found with no surrounding activity, simulating the epitheliated cavity found occasionally in an old clinical case of abscess of the lung when the infection has burned itself out but has left a defect too great for nature to repair.

It is interesting to note that the incidence of fatal empyema was only 10 per cent in animals into which a vein segment was introduced, as

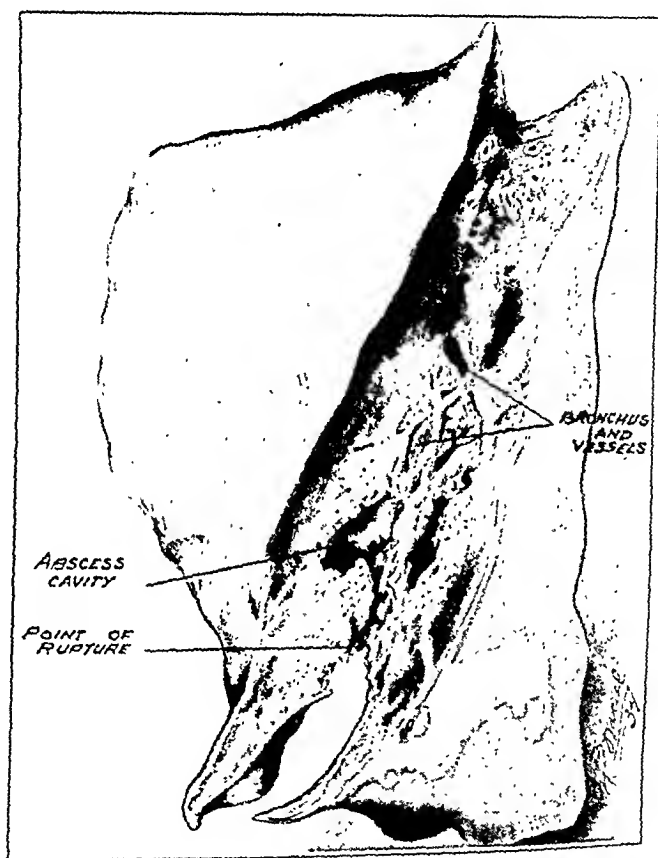


Fig. 3.—A pulmonary abscess which ruptured into the pleural cavity, producing empyema which was fatal.

against the incidence of 33 per cent in animals into which the organisms were introduced in clotted blood as emboli. It is also interesting to note that fatal pulmonary hemorrhage occurred in 5 per cent of the animals into which a vein segment was introduced as against an incidence of 19 per cent in those into which a blood clot was introduced. These facts point out the ability of pulmonary tissue to acquire greater local resistance when not subjected to a sudden overwhelming bacterial invasion simultaneously with the damage produced by the infarction.

Tuttle and Nicoll<sup>28</sup> showed the effect of ligation of the pulmonary artery on the healing time of experimental abscess of the lung. Holman, Mathes and Reichert<sup>29</sup> demonstrated clearly that the occlusion of a branch of the pulmonary artery to a pulmonary lobe leads invariably to marked dilatation of the bronchial artery to that lobe, so that the pulmonary artery in the embolic area is eventually fully supplied

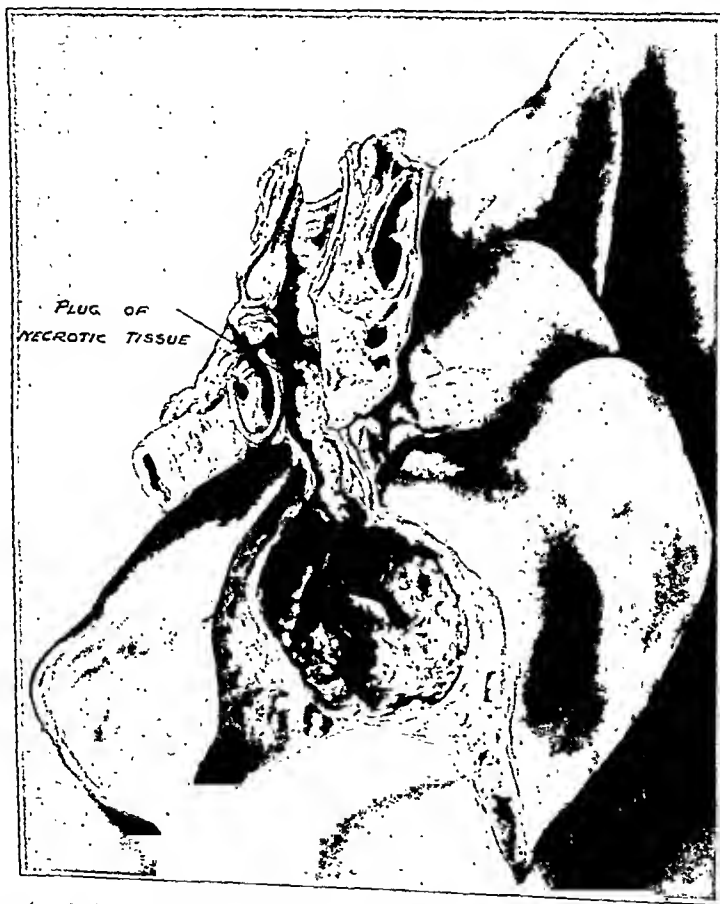


Fig. 4.—A large cavity of a pulmonary abscess produced by an embolus containing the mixed flora of pyorrhea alevolaris which had been stepped up in virulence by animal-to-animal passage. The animal died of toxemia.

with blood. This is brought about usually by the dilatation of the bronchial artery and occasionally by the establishment of capillary

28. Tuttle, W. M., and Nicoll, G. L.: Effect of Pulmonary Artery Ligation on the Healing Time of Experimental Pyogenic Lung Abscesses in Dogs, *J. Thoracic Surg.* 2:60 (Oct.) 1932.

29. Holman, E.; Mathes, M. E., and Reichert, F. L.: A Study of the Bronchial, Pulmonary and Lymphatic Circulations of the Lung Under Various Pathologic Conditions Experimentally Produced, *J. Thoracic Surg.* 1:339 (April) 1932.

anastomosis with the branch of the pulmonary artery adjoining the infarcted area. Those workers also showed that the bronchial artery is invariably dilated to a marked degree in the presence of an infected embolus. This is undoubtedly an important factor in accounting for the difference in the course of the suppurative lesions in the two groups. It is interesting to note the close clinical parallelism in the fact that



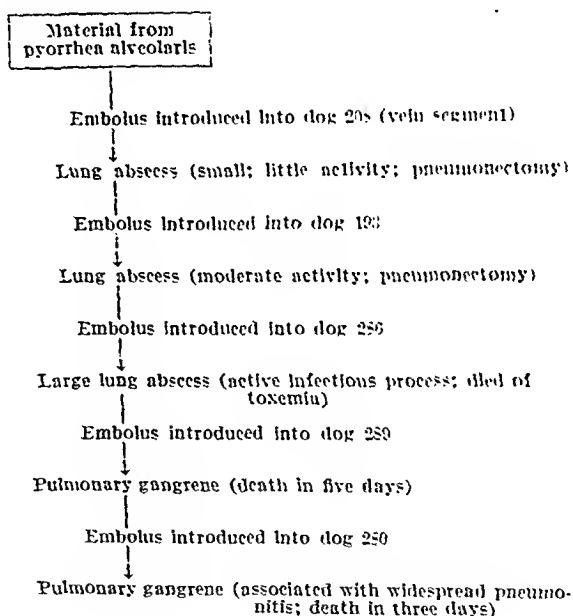
Fig. 5.—Pulmonary gangrene produced by an embolus containing the mixed flora of pyorrhea alveolaris which had been stepped up to the highest virulence. Note the diffuse cavitation and the definite line of demarcation.

in two of the animals there developed signs of cerebral embolism one hundred and twenty and one hundred and fifty days after the implantation of the emboli.

A series of experiments was then planned to determine the relation of the virulence of the mixed bacterial flora to the clinical course of

pulmonary suppuration. Table 4 indicates clearly the gradual stepping up in virulence produced by animal-to-animal passage of infectious material derived from a patient with chronic pyorrhea alveolaris. At first only a small abscess of the lung was produced, with little activity. The lung was removed by pneumonectomy, and a small portion of the contents of the abscess were transplanted in a vein segment as an embolus into dog 193, in which there developed a somewhat larger abscess which displayed moderate activity. The material from this animal was passed on to dog 286, in which there developed a large

TABLE 4.—Results of Experiments Showing Stepping Up of the Virulence of Mixed Bacterial Flora



abscess of the lung; the dog died of toxemia. In the next animal typical pulmonary gangrene developed, and death occurred in five days. Autopsy revealed pulmonary gangrene which was lobar in distribution and accompanied by widespread cavitation (fig. 5). The last animal of the series died in three days of pulmonary gangrene associated with widespread pneumonitis. In short, we noted the entire transition in virulence of the mixed flora from that producing a small area of localized necrosis (pulmonary abscess) to that producing diffuse pulmonary gangrene. Since the flora remained the same, the differences were due to a stepping up of the virulence of the separate organisms.

Having compared the relation of the various modes of bacterial invasion and having studied the relation of the virulence of the mixed

bacterial flora to the pathogenesis and type of pulmonary pathologic process produced, we isolated the various organisms from the mixed bacterial flora and grew them in pure culture. Elaborate aerobic and

TABLE 5.—Results of Experiments with Embolic Implantation of Organisms in Pure Culture (Series 1)

Experiment	Dog	Organisms	Embolus Located by Roentgen Examination	Findings in Resected Lung	Time Since Implantation, Days
1	224	Culture A	Yes	No lesion demonstrable	48
2	200	Culture B	Yes	No lesion demonstrable	50
3	320	Culture C	Yes	No lesion demonstrable	52
4	321	Culture D	Yes	No lesion demonstrable	52
5	301	Culture E	Yes	No lesion demonstrable	53
6	322	Culture F	Yes	No lesion demonstrable	54
7	323	Culture G	Yes	No lesion demonstrable	56
8	324	Culture H	Yes	No lesion demonstrable	57
9	325	Culture I	Yes	No lesion demonstrable	59
10	326	Culture J	Yes	No lesion demonstrable	59
11	279	Culture K	Yes	No lesion demonstrable	60
12	319	Culture L	Yes	No lesion demonstrable	62

TABLE 6.—Results of Experiments with Embolic Implantation of Organisms in Pure Culture (Series 2)

Experiment	Dog	Organisms	Cause of Death	Lesion Found at Autopsy	Time Since Implantation, Days
1	50	<i>B. coli</i> (virulent)	Killed	Area of fibrosis in lung	47
2	50	Culture A	Killed	Small area of fibrosis in lung	83
3	52	Culture B	Killed	Small area of fibrosis in lung	83
4	51	Culture D	Pneumonitis	Diffuse pneumonitis (right lung)	3
5	54	Culture E	Killed in fight	Area of fibrosis (no activity)	44
6	46	Culture F	Killed	No lesion	122
7	71	Culture G	Killed	Area of fibrosis (no activity)	70
8	80	Culture H	Killed	No lesion	79
9	104	Culture J (anaerobic hemolytic streptococcus)	Killed	Small area of fibrosis	190
10	107	Culture K ( <i>Spirochaeta microdentium</i> in agar cubes)	Killed	No lesion demonstrable	151
11	108	Culture L ( <i>Spirochaeta macrodentium</i> in vein segment)	Killed	No lesion demonstrable	150
12	109	Culture M (anaerobic; in abscess of lung of patient)	Killed	No lesion demonstrable	147
13	102	Culture N ( <i>Bacterium melaninogenium</i> ; anaerobic hemolytic streptococcus)	Killed	No lesion demonstrable	180

anaerobic cultures (prepared by a method described by Herrmann<sup>30</sup>) were made on special mediums, with the pabulum require-

30. Herrmann, Louis G.: An Improved Method for the Cultivation of Anaerobic Microorganisms, *J. Bact.* 23:331 (April) 1932.

ments and hydrogen ion concentration to meet the specific demand of each organism. Two separate strains of aerobes and anaerobes (used in producing abscess of the lung) were plated out. The organisms grown in pure culture were introduced individually in vein segments into two new series of animals. The emboli were located by roentgenograms and their position was rechecked by weekly roentgen examination. In one series the animals were killed. In the other series, in which the animals were spared, the lung in which the embolus had lodged, as checked by roentgen examination, was removed by pneumonectomy from forty-eight to sixty-two days after implantation. In no animal of either series could an abscess be noted (tables 5 and 6).

Our next step will be to determine which combination of these organisms has a proteolytic action on tissue *in vitro*. The effect of these combinations will then be studied *in vivo*. Later emboli containing the various proteolytic combinations will be introduced into the jugular vein of dogs, and the action of respective combinations on pulmonary tissues will be studied in an attempt to find out which group of organisms produces clinical abscess of the lung. It is hoped that time permits us to combine the embolic and intrabronchial lines of attack in the attempt to determine, if possible, the organisms or group of organisms which act as the vanguard, preparing the way for the advance of the necrotizing proteolytic bacterium or group of bacteria. Through this maze of experimental work, we have the patient as our guide. To this end we hope to make clinical application of the phenomena of desensitization as studied and applied by Dorst and Wherry.<sup>31</sup>

#### SUMMARY AND CONCLUSIONS

The various concepts of the etiology of pulmonary suppuration have been reviewed. The bacteriologic studies of numerous clinical abscesses of the lung reveal bacterial flora similar to that of an unhygienic buccal cavity. This similarity of organisms suggests aspiration as the possible cause. However, the relative infrequency of pulmonary abscess as against the frequency of bronchial contamination following operations on the upper respiratory passages may be taken as the strongest argument against the hypothesis of aspiration as the source of infection.

Experimentally it has been demonstrated that the lungs are susceptible to the formation of abscesses from septic embolism but are

---

31. Dorst, S., and Wherry, W. B.: *Local Skin Reactions in the Selection of Antigens for Autogenous Vaccines*, Ohio State M. J. **24**:539 (July) 1928. Wherry, W. B.: *Hypersensitivity to Bacterial Proteins and Its Rôle in Susceptibility and Immunology*, Am. J. Hyg. **14**:539, 1931.

very resistant to bronchogenic inoculation. Certain abscesses are purely embolic and others are purely bronchogenic, but a great number are not explained by either mode of origin. For these a combination of both mechanisms may eventually account for the disparity between the existing bacterial flora of the abscess and that of the operating field. Pulmonary abscess may be pictured bacteriologically as originating from an uncertain agent but ending in a definite clinical picture that includes a terrific secondary invasion of organisms of various and diverse types. The theories with regard to specific initial infection rest on very uncertain data.

Cognizant of the scope of this problem, we laid out a detailed and well controlled group of experiments. To contrast the modes of bacterial invasion in relation to the pathogenesis of the lesion, the endobronchial and the embolic approach were tried. In sixteen animals the material (scrapings from the gingival trenches of persons with pyorrhea alveolaris) was introduced into the secondary and tertiary bronchi by means of a bronchoscope. In spite of the fact that the cough reflex was abolished and the bronchus occluded with the plug, in no case did a pulmonary abscess develop. In two of the animals signs of early bronchial ulceration and dilatation were noted beyond the point of occlusion of the bronchus by the cotton plug. In two other animals the material was introduced into the frontal sinus. No abscess was produced. In a series of forty animals, the infectious material was introduced in the form of emboli (vein segment or blood clot). In this series 92.5 per cent of the animals were found to have an abscess of the lung at autopsy. The abscesses produced varied from acute abscesses found in animals dying of empyema or of pulmonary hemorrhage to chronic abscess of from one hundred and ten to two hundred and thirty days' duration. The incidence of death caused by empyema in the group receiving the vein segments was 10 per cent, as against 33 per cent in the group receiving the blood clots. The incidence of fatal pulmonary hemorrhage was 5 per cent in the former group as against 19 per cent in the latter. These facts point out the ability of pulmonary tissues to develop (through secondary dilatation of the bronchial arteries, etc.) an excellent local protective mechanism when not subjected to a sudden overwhelming bacterial invasion simultaneously with the damage produced by the infarction.

In another series of experiments planned to determine the relation of the virulence of the mixed bacterial flora to the clinical course of pulmonary suppuration, the complete transition in virulence was noted from that producing a small area of localized necrosis (pulmonary abscess) to that producing diffuse pulmonary gangrene. The stepping up in virulence was accomplished by animal-to-animal passage of the organisms.

Two distinct mixed bacterial strains used in producing pulmonary abscesses were plated out, and the separated aerobes and anaerobes grown in pure culture were introduced individually in vein segments into two series of animals. But in no animal of either series did a chronic abscess of the lung develop. At present studies are being made of the action of various combinations both in vitro and in vivo in an attempt to determine, if possible, the exact nature of their synergistic bacterial action.



# MESENTERIC LYMPHADENITIS SIMULATING ACUTE APPENDICITIS

## QUANTITATIVE STUDY OF THE SIZE OF NORMAL MESENTERIC LYMPH NODES

CHARLES H. MEAD, M.D.

DULUTH, MINN.

Enlargement of the lymph nodes of the mesentery has been recognized since the eighteenth century. Bertein and Worms credited Sydenham with the earliest description of mesenteric tumors or enlargements in children. The term "strumous abdomen" was used during the early nineteenth century to describe the condition. "Tabes mesenterica," a term which has endured, was first introduced in 1775 by Ball.

The diagnosis of the disease during life was usually a conjecture, and it was recorded as a fact only when the disease was seen at autopsy. All necropsy observations during this early period indicated that the process was tuberculous. The condition was not commonly recognized at the beginning of the twentieth century, and was regarded as a pathologic curiosity as recently as 1905 (Branson). Mächtle, in 1909, published the first summary from the surgical literature, and only fourteen cases were recorded. The paucity of cases undoubtedly accounts for the relatively little attention which the disease process attracted.

During the early years of the twentieth century, however, the condition began to provoke surgical attention. This was probably because of the increased frequency with which surgical exploration of the abdomen was performed for the relief of acute disease processes. Enlargement of the mesenteric lymph nodes was frequently encountered as the only etiologic factor in the production of acute abdominal symptoms. Cases were described by Richardson wherein the symptoms were those of acute appendicitis, but which revealed on surgical exploration merely an enlargement of the mesenteric lymph nodes and no appendical pathologic condition. Some of the enlarged nodes showed caseation, suppuration or calcification, while others appeared to be only mildly inflamed. All the nodes were thought to present a tuberculous process (Branson; Corner, 1905 and 1908; Shiota; Fordyce; Thiemann; Newbolt; Floderus; Lund; Still; Carson; Iselin). Consequently, the condition soon received attention as a distinct surgical entity.

---

From the Departments of Surgery and Anatomy, the University of Minnesota, Minneapolis.

A brief description of such a case encountered in the surgical service of the University of Minnesota Hospital will serve as an illustration of the disease process.

#### REPORT OF A CASE

*History.*—A white boy, 2.5 years of age, was admitted to the University of Minnesota Hospital on July 19, 1929, and discharged on July 27. The patient was well until two weeks before admission, when marked anorexia developed. Six days before entrance he complained of abdominal pain, and the mother thought that he had a fever. Four days later he complained of more severe pain, which he localized in the right lower quadrant of the abdomen. There had been neither nausea nor emesis. Defecations had been regular and the stools normal. A physician was consulted, who found the child to have a temperature of 102 F. and marked tenderness in the right lower quadrant of the abdomen. The child was immediately referred to the University Hospital with a diagnosis of acute appendicitis. The remaining history was normal as was the family history.

*Physical Examination.*—The child appeared to be well developed and well nourished. Respirations were somewhat labored. The temperature was 102 F., and the pulse rate was 120. There was neither localized nor generalized lymphadenopathy. Cardiac and pulmonary observations were normal. The abdomen was prominent, and was tense on palpation. Tenderness was noted in the right lower quadrant, but muscle spasm and rigidity were questionable. There were no palpable abdominal masses, and shock *en retour* was absent. A rectal examination revealed no abnormalities.

*Laboratory Data.*—The urine was normal except for a few white blood cells in the urinary sediment. Examination of the blood showed: hemoglobin content, 72 per cent; red cell count, 4,350,000, and white cell count, 13,000, with polymorphonuclear neutrophils 51 per cent and lymphocytes 49 per cent. A roentgen examination of the chest showed no pathologic process.

*Diagnosis and Therapy.*—A diagnosis of acute appendicitis was made, and an operation was immediately performed. Numerous large, hard lymph nodes were noted throughout the mesentery of the small intestine, on opening the anterior abdominal wall through a McBurney incision. One group of nodes in the mesentery of the ascending colon felt like a lobulated kidney. The nodes were about 1 cm. in diameter, and presented a congestion of the vessels and a puckering of the peritoneum about them. Most of the large, hard nodes were found along the intestinal border of the mesentery. The appendix was normal in gross appearance. Appendectomy was done, but no biopsy was taken of the enlarged nodes. The postoperative diagnosis was that of acute adenitis of the mesenteric lymph nodes, of unknown origin. Histologic examination of the appendix showed it to be normal.

*Postoperative Course.*—The child's immediate convalescence was uneventful, and he was discharged from the hospital on the eighth postoperative day. He was not seen again until 2.5 years later, when he entered the University of Minnesota outpatient dispensary complaining of recurrent attacks of abdominal distress associated with emesis and diarrhea. The attacks occurred at intervals of about two months. The child's mother stated that he seemed to become fatigued easily. Further investigation of the history showed that the child had ingested milk from tuberculous cows a short time before the onset of the original acute abdominal symptoms.

In view of this history and the previous operative findings a Mantoux test was applied, and the result was positive. An x-ray picture of the abdomen was taken, which showed calcified mesenteric lymph nodes (fig. 1). Consequently the final diagnosis was tuberculosis of the mesenteric lymph nodes.

#### TUBERCULOUS MESENTERIC LYMPHADENITIS

*Frequency.*—The frequency of occurrence of tuberculous mesenteric lymph nodes has not been studied extensively. The earliest chrono-



Fig. 1.—A roentgenogram showing the calcified mesenteric lymph nodes mentioned in the description of the case of tuberculous mesenteric lymphadenitis.

logical investigations of this disease entity were based on observations of the condition at autopsies on tuberculous subjects and not on clinical considerations. Its frequent occurrence stimulated several studies of the relationship of tuberculous mesenteric lymphadenitis to tuberculosis elsewhere in the body (Rilliet and Barthez; Woodhead; Colman; Carr; Branson; Fordyce; Still). The condition was found to exist in as high as 79 per cent of cases with other primary tuberculous foci. Studies of the relationship of gastro-intestinal tuberculosis to tuberculosis

in other regions were undertaken at about the same time (Eisenhart; Haman; Conrath). The investigations showed that gastrointestinal tuberculosis was present in as many as 68 per cent of persons with tuberculosis in other parts of the body. A comparison of these figures suggested a relationship between tuberculosis of the digestive tract and tuberculosis of the mesenteric lymph nodes.

The frequent presence of tuberculous mesenteric lymphadenitis at autopsies on persons with tuberculosis stimulated investigations of its occurrence in general autopsy observations. Reports of several series of cases show the incidence of tuberculous mesenteric lymphadenitis to vary from 1 to 3 per cent (Osler and McCrae). The prevalence of the condition varies with the region of the world from which the figures were derived, the higher figures coming from certain sections of Scotland.

Finally, the incidence of the condition in general abdominal surgical practice was studied. It would be expected to be higher than that in general autopsy observations, because most abdominal explorations are based on the presence of intra-abdominal pathologic conditions. One investigation of this phase of the problem has been recorded in the literature (Braithewaite). The study covered a period of twelve years, during which time the surgeons were admonished to look especially for the condition. One would expect the ultimate figure of frequency to be higher than that derived from mere casual recognition of the condition; nevertheless only 0.74 per cent of 58,731 exploratory laparotomies showed evidence of tuberculous mesenteric lymphadenitis.

From the foregoing analysis it may be concluded that the occurrence of tuberculous mesenteric lymphadenitis is infrequent in general clinical experience. It is true that no large series of clinical cases has been reported. A good share of the literature concerning the frequency of occurrence of this clinical condition consists of reports of cases. Mächtle published a summary of fourteen cases from the surgical literature in 1908. Floderus published data in 1912 concerning eighteen cases of enlargement of mesenteric lymph nodes which he obtained during the preceding decade. Riseley described thirty operative cases in 1915, and Carson, in 1919, reported fifty operative cases encountered during an eight year period. Mettenleiter reported twenty-nine operative cases obtained over a ten year span, Ljunggren described sixty cases of mesenteric lymphadenitis encountered during four years, and Bagg reported thirty cases seen over an eight year period. Thus, it may be concluded that the scant study given the condition is due to its relatively infrequent occurrence.

*Age.*—Infancy and childhood are the periods of life in which tuberculosis of the mesenteric lymph nodes is most frequently encountered (Colman; Carr; Branson; Corner, 1905; Floderus; Lund; Parker;

Carson; Walker; Braithewaite; Osler and McCrae; Bell; Marshall). The condition is sometimes seen in young adults (Newbolt; Floderus; Riseley) and occasionally in the middle-aged, but by far the greatest number of cases are seen in children from the time of birth to 15 years of age.

*Symptomatology.*—No precise clinical syndrome for tuberculosis of the mesenteric lymph nodes has been established. The varying symptoms have been well described by many writers, but they differ somewhat in children and adults (Corner, 1905 and 1912; Floderus; Franke; Carson; Clute; Krogsgaard; Braithewaite; Ljunggren; Mettenleiter; Bagg; Auchincloss).

The condition may be present in either an acute or a chronic form. The acute type is usually marked by a sudden onset and complaints of severe, crampy abdominal pain, followed by nausea and emesis. The pain commences in the epigastrium or is generalized over the abdomen and localizes in the right lower quadrant. It is paroxysmal and sufficiently severe to cause the patient to double up and cry out. The attacks commonly occur from two to five times a day, and vary in duration from five minutes to two hours. The pain usually ceases as suddenly as it began, and all symptoms subside in two or three days.

Patients presenting the more chronic form complain of vague, intermittent, transitory attacks of colicky pain in the right lower quadrant or other regions of the abdomen. Often the complaint is not of pain but merely of a sensation of drawing or dragging in the abdomen. There is frequently a history of repeated attacks of indefinite gastric distress associated with nausea and emesis. Constipation and diarrhea are not common symptoms in the chronic form, but may be present in the acute attack. The chronic form is more common in young children, and the condition ultimately becomes acute.

The symptoms in older children and young adults are usually the same as those just described, but the clinical picture in the more advanced age group may be complicated by symptoms of dysphagia (Wakely), peptic ulcer (Thiemann; Lund; Bier; Keppler and Erkes; Davidovitch; Ljunggren; Golden and Reeves), biliary colic (Most; Pribram), intestinal spasm (Schalij), constipation or diarrhea (Sternberg), renal colic or hematuria (Schmieden; Walker; Davidovitch; Golden and Reeves) or even sciatica (Ljunggren).

*Physical Findings.*—Physical examination reveals abdominal tenderness and spasm and rigidity of the muscles over the tender area. The pain is frequently localized just to the right of the umbilicus above McBurney's point (Gehrels; Brentano; Auchincloss). Occasionally a mass may be palpated in the right lower quadrant of the abdomen (Floderus; Riseley; Braithewaite; Bagg). Rebound tenderness is common. Lymph nodes elsewhere in the body usually are not enlarged.

Rectal examination reveals no abnormalities. The pulse rate varies from 100 to 120, and the temperature is elevated from 100 to 104 F. (Fordyce; Bell). The general impression is that of a pronounced systemic reaction without the marked clinical findings one expects.

*Laboratory Data.*—Examination of the urine generally shows it to be normal. The white blood cell count varies from 12,000 to 17,000, the differential count showing about 80 per cent polymorphonuclear neutrophils.

*Diagnostic Aids.*—Roentgen examination of the abdomen often discloses the presence of calcified mesenteric lymph nodes. This procedure was used as early as 1905 by Corner for the diagnosis of tuberculosis of the mesenteric lymph nodes. It had received little attention in the literature as a diagnostic procedure, however, until the recent work of Strömbeck. He expressed the belief that the presence of calcified mesenteric lymph nodes is strongly indicative of tuberculosis, as such calcifications arise early and almost exclusively after the onset of a tuberculous process. In infants and young children it is common to find the Pirquet reaction positive (Head). It is now generally recognized, however, that a Pirquet reaction fails to occur in a fairly large percentage of persons known to be tuberculous. The incidence of positive skin reactions with tuberculin should be considerably higher therefore, following the widespread use of the more sensitive Mantoux intradermal test.

*Diagnosis.*—The differential diagnosis in children includes, primarily, acute appendicitis and, secondarily, Meckel's diverticulitis, intussusception and pyelonephritis. In older children and young adults the condition closely simulates acute appendicitis, but must also be differentiated from cholecystitis and cholelithiasis, pyelonephritis and intestinal and peritoneal tuberculosis.

*Treatment.*—The treatment is always surgical exploration of the abdomen when the symptoms are acute. Simple exploration seems to do no harm in these cases, and often has a beneficial effect whether or not any further procedure is done (Ungar; Bell). Surgical opinion varies as to the advisability of removing or leaving the enlarged mesenteric nodes, as both procedures have been successful (Head; Bell). Newbolt recorded an instance, however, when failure to remove the largest nodes necessitated a secondary laparotomy to remove them before relief of symptoms was obtained. More radical measures are seldom necessary, although a few cases are reported in which abscessed nodes were scraped out (Gehrels) or ileotransversostomy or intestinal resection was performed (Strömbeck).

*Complications.*—The disease process may result in diverse complications originating from the primary disease of the lymph nodes.

Calcification of nodes overlying the ureters may result in compression of the ureter with symptoms of disease of the urinary tract such as hematuria, frequent and painful micturition and abdominal pain simulating ureteral colic (Schmieden; Walker; Davidovitch; Golden and Reeves). The acute process sometimes results in the perforation and rupture of a caseous gland (Floderus; Edén; Iselin; Head; Bagg; Bell; Grinn). intestinal obstruction (Floderus; Jones; Brüning; Homuth; Wakely; Head; Gutzeit; Koschucharoff; Hubrich; Mischel), compression of the pylorus or duodenum (Floderus; Keppler and Erkes; Matyas; Orth; Wantoch), acute ileus (Floderus; Carson; Homuth), intra-abdominal abscess (Edén; Iselin; Head; Bagg), hydro-nephrosis (Hepburn; Valentin), obstruction of the biliary ducts (Floderus; Jean), obstruction of the portal vein with associated ascites (Floderus), erosive bleeding from large intra-abdominal vessels (Whitworth; Ruescher; Rawitzkaja; Fischmann), and thrombosis in the mesenteric vessels (Murray).

*Mechanism of Infection.*—The exact mechanism by which the mesenteric lymph nodes become infected with tuberculosis has not been demonstrated. The tuberculous intestinal tract has been the most obvious source of infection. The digestive tract has also been considered as the probable route through which tubercle bacilli in infected foods have been transmitted to the mesenteric lymph nodes. Infected sputum and milk have been most commonly accused as vehicles in the transmission of the organisms to the gastro-intestinal tract and to the lymph nodes of the mesentery (Branson; Braithewaite; Head). It is stated that tuberculosis of the intestinal tract is rare in the first years of life, after which it increases in frequency to the fourth or fifth years (Opie). It has been pointed out that the increase in the number of gastro-intestinal infections is coincident with the average time of weaning, and that this is probably due to a change in diet through which contaminated foods may invade the intestinal tract. This theory of infection of the digestive tract with relation to the age period is of significance in considering the sources and routes of infection of the mesenteric lymph nodes.

Intestinal stasis associated with distention and catarrhal inflammation with abrasions of the mucous membrane have been mentioned as producing portals of entry to the mesenteric lymph nodes (Bell). It has been suggested that the resistance of the mucosa is lessened by the absorption of intestinal toxins, thus permitting the passage of organisms (Thiemann; Carson). Others believe that organisms may pass through the intact mucosa (Walsham; Morley; Philip). The latter view is not generally accepted. Trauma and intestinal parasites have also been considered as etiologic factors (Bell; Wagner). The constant involvement of nodes draining the region of the appendix has frequently sug-

gested tuberculosis of that organ. Although tuberculosis of the appendix occurs in from 2 to 5 per cent of abnormal appendixes (Lennander and Nyström), no clear case with associated mesenteric lymphadenitis has been recorded. Recent investigations indicating that tubercle bacilemia may be present shortly after the onset of a tuberculous infection any place in the body favor a hematogenous route of infection (Sata: Löwenstein, 1930 and 1931).

*Pathology.*—The pathologic process in the tuberculous mesenteric lymph node does not deviate from its usual manifestations; thus, the findings are dependent on the stage of the disease. The progress of the condition is probably governed by the virulence of the organism and the resistance of the individual subject.

The principal lesions noted at operation are: enlarged, inflamed, discrete nodes; masses of nodes grouped around a central suppurative or caseous node, or small, scattered, calcified glands (Braithwaite; Bell). In the later stages of softening, caseation, calcification and formation of scars, the disease condition is easy to recognize, and it is usually not confused with any other. In early stages, however, its gross recognition is difficult, and consequently requires microscopic examination or inoculation of guinea-pigs with the tissue for its decisive identification. The importance of the inoculation of guinea-pigs as a final diagnostic measure, after gross and histologic examination of the tissue, is emphasized by the experimental work of MacFadyen and MacConkey and of Bartel. Mesenteric lymph nodes showed, in these studies, the presence of tubercle bacilli in 25 per cent of a series of nontuberculous cases brought to autopsy, in which the lymph nodes appeared normal on gross and histologic examination, and in which there was neither clinical nor autopsy suggestion of tuberculosis elsewhere in the body.

Tuberculous mesenteric lymphadenitis most frequently affects the nodes which drain the ileocecal region (Corner, 1905; Braithwaite). Almost any node or group of nodes within the mesentery of the small intestine may be involved, however, because of their close anatomic relationships. In many instances the disease may be localized in the primary group of nodes at the margin of the intestine or at the root of the mesentery. Frequently the pathologic process is confined to the ileocecal group of nodes. In practically every instance the disease involves the nodes along the ileocolic artery to some extent (fig. 2).

*Causation of Pain.*—The symptoms of pain, spasmodic mild abdominal distress, nausea, emesis and diarrhea can probably be explained as being due to acute alterations in and about the mesenteric nodes. Wilms and Kappis showed that sensations of pain can be elicited within a field extending from the root of the mesentery to its free border, especially along the vessels. The mesenteric nodes are situated



chiefly along the vessels, and consequently stretching of the peritoneum from acute swelling and scarification or, later, calcification of the nodes

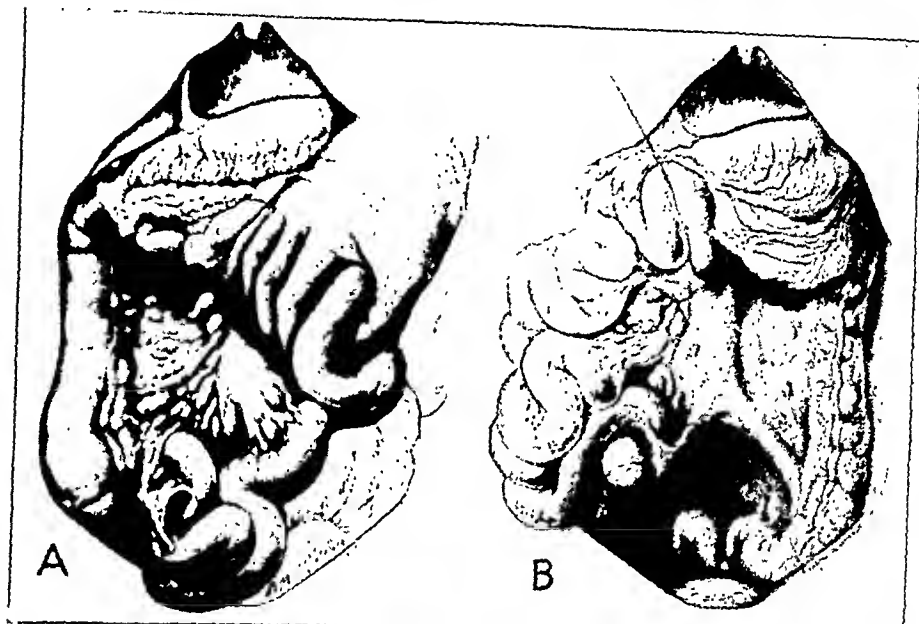


Fig. 2.—*A*, enlarged, discrete lymph nodes similar to the kind often noted at operation. The right side of the mesentery is exposed, and the location of the enlarged nodes along the course of the larger blood vessels is well shown. *B*, enlarged, discrete lymph nodes when seen from the left side of the mesentery. From L. P. Bell (*Surg., Gynec. & Obst.* 45:465, 1927).



Fig. 3.—A calcified lymph node with associated puckering and scarification of the overlying peritoneum. It is evident that calcified spicules are also present, which might project into and irritate the surrounding peritoneum. From L. P. Bell (*Surg., Gynec. & Obst.* 45:465, 1927).

involving the overlying peritoneum (fig. 3) could easily be considered as causative factors in the production of painful sensation (Valentin;

Braithewaite; Davidovitch; Golden and Reeves; Auchincloss). Colic-like pains have been ascribed to intestinal spasms and partial invaginations (Carson; Gray; Braithewaite).

*Prognosis.*—The prognosis of mesenteric lymphadenitis with regard to freedom from symptoms is fair. Strömbeck observed fifty-five patients after operative exploration over a period of from six to twelve years, thirty (55 per cent) of whom were free from symptoms. The early literature shows a high mortality in mesenteric lymphadenitis, for in a series of fifteen operative cases Floderus had a mortality of 33 per cent. Recent reports of larger series of cases, however, showed no operative mortality (Bagg; Strömbeck).

#### NONTUBERCULOUS MESENTERIC LYMPHADENITIS

The literature regarding mesenteric lymphadenitis referred almost exclusively to the tuberculous type until 1920. Apparently it had been considered unlikely that the condition might be derived from some other infectious organism. Differentiation of the nontuberculous from the tuberculous type has not been entirely satisfactory, and has been based principally on pathologic and bacteriologic studies. The more recent recognition of nontuberculous enlargement of the mesenteric lymph nodes has led to its clinical classification as a distinct entity. Anderson directed attention to the fact that enlargement of the mesenteric lymph nodes had caused confusion with appendicitis. Wilensky, in 1920, wrote concerning a group of frequently encountered cases in which symptoms of acute abdominal abnormality are presented but in which on exploration only enlarged mesenteric lymph nodes are found. Histologic and bacteriologic study of the enlarged nodes fails to show tuberculosis, but shows simple lymphoid hyperplasia and pyogenic organisms. Pathologically and bacteriologically the processes are pyogenic. Clinically the condition cannot be demarcated from tuberculous mesenteric lymphadenitis, nor from acute appendicitis.

The following description is that of a case of nontuberculous mesenteric lymphadenitis encountered in the surgical service of the University of Minnesota Hospital.

*History.*—A white girl, 9 years of age, was admitted to the University of Minnesota Hospital on July 16, 1925 and was discharged on July 29. The child was well until approximately one year before admission. At this time she began to complain of intermittent, dull pain somewhat localized in the epigastrium. The appetite remained good, however, and there had been no nausea, emesis, diarrhea or constipation. The mother thought that the child had a fever at times, but no temperatures had been recorded.

Two days before admission to the hospital the patient was seen by a physician because of marked abdominal pain. At this time the temperature was 100 F. A diagnosis was made of acute appendicitis, and the child was removed to the University of Minnesota Hospital for care.

The history showed that the child had complained for three years of intermittent urinary frequency and burning. She had pneumonia twice and influenza on one occasion. The family history was irrelevant.

*Physical Examination.*—The child appeared to be well developed and well nourished. The pulse rate was 110 and the temperature 99.8 F. The remainder of the examination revealed no abnormality except in the abdomen, where tenderness was present on palpation in the right lower quadrant, without muscle spasm or rigidity. Rectal examination revealed more tenderness on the right than on the left. No lymphadenopathy or abdominal masses were noted.

*Laboratory Data.*—The urine was normal except for a few epithelial and white blood cells; the hemoglobin was 72 per cent, and the white blood cell count 17,250, with a differential count of polymorphonuclear neutrophils 72 per cent and lymphocytes 28 per cent.

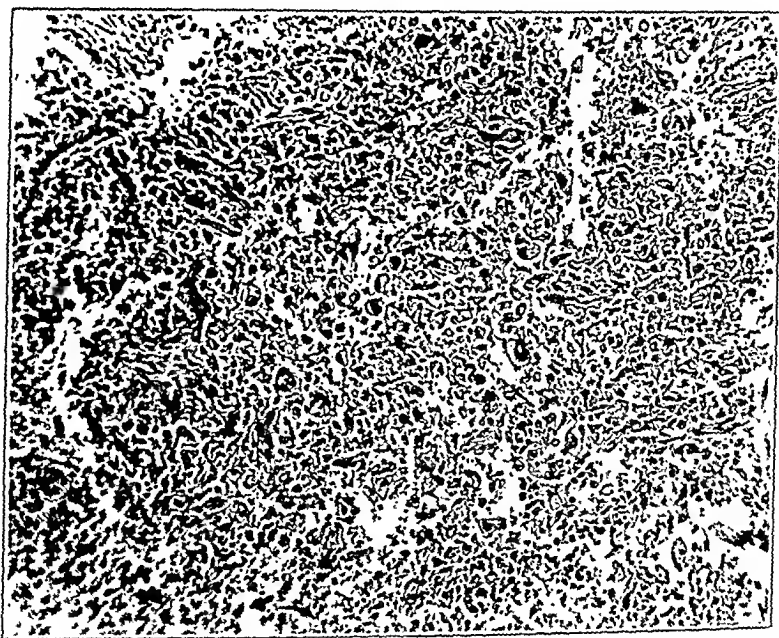


Fig. 4.—A photomicrograph of a section of the lymph node removed at operation in the case of nontuberculous mesenteric lymphadenitis. Simple lymphoid hyperplasia is shown;  $\times 100$ .

*Diagnosis and Therapy.*—In view of the urinary history a diagnosis of pyelitis was strongly considered. Appendical involvement could not be ruled out, however, and exploratory laparotomy was performed. The appendix appeared to be normal by gross examination, but marked adenopathy was noted throughout the entire mesentery. The appendix and one of the enlarged nodes were removed for histologic examination. Microscopic examination of the appendix revealed no abnormalities, and study of the lymph node showed simple lymphoid hyperplasia (fig. 4). The final diagnosis was nontuberculous mesenteric lymphadenitis.

*Postoperative Course.*—The child's postoperative convalescence was uneventful. Observers in the University of Minnesota outpatient dispensary noted three years later that the child had had no exacerbations of symptoms. Roentgen examination of the abdomen showed no calcified mesenteric lymph nodes, and reaction to the Mantoux test was negative.

*Frequency.*—Publications dealing with the condition as an entity are relatively few, and consequently the frequency of occurrence of the condition has not been widely studied. The disease is thought to be common, but unrecognized (Struthers; Freeman; Heusser; Wilensky and Hahn; Short). Its incidence has been determined in one series of two hundred laparotomies, in which it was found to occur in 6 per cent of the cases (Short). This would indicate a much greater frequency than of tuberculous mesenteric lymphadenitis.

*Age.*—Nontuberculous mesenteric lymphadenitis is essentially a disease of children, the age period ranging from birth to 15 years (Wilensky; Struthers; Freeman; Short). The condition has been recorded in young adults, but is far more common in the preadolescent period (Struthers). Heusser, Guleke and Sennels presented reports of more than two hundred cases of mesenteric lymph node hyperplasia, occurring chiefly in patients between the ages of 10 and 20 years.

*Symptomatology.*—It is stated that nontuberculous mesenteric lymphadenitis may simulate any acute abdominal condition for which laparotomy is commonly performed (McFadden). The condition assumes both acute and chronic forms (Wilensky; Struthers; Freeman; Wilensky and Hahn; Short). The symptoms in the acute type simulate those of acute appendicitis so closely that they cannot be differentiated. The patient usually complains of sudden, crampy, colicky, abdominal pain, which is first diffuse about the umbilical region, later localizing in the right lower quadrant of the abdomen, or just to the right of the umbilicus. The pain commonly ceases as suddenly as it began, and is recurrent. There may be associated nausea and emesis, constipation or diarrhea. In the chronic form there is commonly a history of a long period of loss of energy and weight with associated fleeting gastric and abdominal distress, and finally a suddenly precipitated acute abdominal pain.

*Physical Findings.*—Physical examination generally shows a definite area of abdominal tenderness, cutaneous hyperesthesia, muscle spasm and rigidity over the tender area, and often rebound tenderness. Usually no masses are palpated, and results of a rectal examination are negative. The pulse rate is slightly increased, and the temperature varies from 99 to 104 F. (Freeman; McFadden).

*Laboratory Data.*—Results of laboratory examination are usually negative except for a white blood cell count which usually varies from 12,000 to 17,000, 80 per cent of the cells being polymorphonuclear neutrophils.

*Diagnosis.*—The condition must be differentiated from the acute abdominal processes common to childhood such as Meckel's diverticulitis, intussusception and pyelonephritis. Nontuberculous lymphadenitis

is almost invariably confused with acute appendicitis, and fails to present any characteristic symptoms which will justify a clinical differentiation of the two conditions.

*Treatment.*—Surgical exploration of the abdomen is the usual treatment of the condition (Wilensky; Struthers; Freeman; Heusser; Wilensky and Hahn; McFadden; Short). There is no unanimity of opinion as to the advisability of excision of the enlarged lymph nodes. In most of the reported cases the nodes have not been disturbed. It is unanimously agreed that the appendix should be removed whether or not it shows a gross pathologic process. Opening the abdomen seems to be efficacious treatment, for in most instances an uneventful recovery ensues.

*Complications.*—Intestinal obstruction and fecal fistulas have been the principal complications associated with nontuberculous lymphadenitis (Wilensky). Both types are rare.

*Mechanism of Infection.*—The mechanism of infection is unknown. Catarrhal conditions and ulcerations of the mucosa have been considered as possible portals of entry for the invading organisms (Freeman; Wilensky and Hahn). Contaminated food and milk have been described as vehicles of infection (Freeman). Intestinal parasites and trauma have been mentioned as possible predisposing factors (Heusser; Wagner). The appendix has been suggested as the most likely portal of entry for the infection (Wilensky). The fact that enlarged mesenteric lymph nodes are not seen in acute appendicitis, and that the appendix is normal in cases of nontuberculous mesenteric lymphadenitis, is thought to be strong contradictory evidence regarding this theory. It is generally agreed that pyogenic organisms are the principal etiologic factors in nontuberculous mesenteric lymphadenitis (Wilensky; Struthers; Freeman; Wilensky and Hahn). This agreement is based on pathologic and bacteriologic studies. The absence of tubercle bacilli has been demonstrated by cultural and antiformin methods and by the inoculation of guinea-pigs (Heusser).

*Pathology.*—The gross appearance of the nodes when seen at operation is somewhat variable (Wilensky; Struthers; Freeman; Wilensky and Hahn; Bell; Short). The early stages of the process consist essentially of enlargement of the affected nodes, which are usually discrete and dull red. The surrounding peritoneum appears to be normal. Early caseation appears as single or multiple small yellow spots on the surface of the reddened node. With this change the surrounding peritoneum shows an extension of the inflammatory process. There may be an increase of peritoneal fluid at this time. The caseation may progress to form a definite abscess of the node or nodes involved. The abscess is usually well walled off, however, but may become extremely

large. Finally, the process may recede and result in a condition of scarification or cicatrization of an area of peritoneum about the previously diseased gland. The final stage of the process is calcification, wherein a hard node is formed possessing multiple spicules which project into and irritate the surrounding peritoneum.

The affected nodes may be scattered through the mesentery. They are usually most prominent, however, along the ileocolic artery or at

TABLE 1.—*A Comparison of the Salient Clinical and Pathologic Features of Tuberculous and Nontuberculous Mesenteric Lymphadenitis*

	Tuberculous	Nontuberculous
Frequency	In general autopsy statistics, 1 to 5% In abdominal laparotomies, 0.54% In autopsies on tuberculous cases, 0.73%	In abdominal laparotomies, 6%
Age	Birth to 15 years	Birth to 15 years
Symptoms	Acute, or chronic which became acute; pain: sudden onset, colicky, intermittent, first generalized or about umbilicus, later localizing in right lower quadrant of abdomen; nausea and emesis	The same
Physical findings	Abdominal tenderness; muscle spasm and rigidity; shock on return; pulse rate, 100 to 120; temperature, 100 to 101 F.; often a positive Pirquet reaction	The same
Laboratory observations	Leukocytosis, 12,000 to 17,000; 80% polymorphonuclear neutrophils	The same
Treatment	Surgical exploration, with or without removal of nodes equally successful, and appendectomy	The same
Complications	Urinary symptoms due to calcified epireteral nodes; abscess and perforation of abscess; intestinal obstruction; acute ileus; hydronephrosis; obstruction of common bile duct or portal vein	The same
Etiology	Tubercle bacilli	Pyogenic or unknown organisms
Source and mechanism of infection	Tuberculosis of digestive tract; infected milk or sputum; organisms passing through normal or eroded bowel wall; tuberculosis of the appendix	Infected milk, sputum, food; diseased appendix; intestinal parasites and trauma as predisposing factors
Pathology	Enlarged, inflamed, discrete nodes; masses of nodes about a central caseous or suppurative node; calcified nodes; scarified peritoneum	The same
Pathologic anatomy	Nodes draining ileocecal region; any place in mesentery, along ileocolic artery	Nodes along ileocolic artery, scattered, along root of mesentery
Prognosis	53 per cent five year cures	87 per cent four year cures

the root of the mesentery. Microscopic examination of the nodes shows only lymphoid hyperplasia.

*Prognosis.*—Strömbeck followed up forty cases for an average of 3.9 years postoperatively and found 87 per cent free from symptoms. The operative procedure had consisted simply of appendectomy. There was no operative mortality.

A comparison of the preceding data, concerning tuberculous and nontuberculous mesenteric lymphadenitis, indicates many points of similarity (table 1). Several writers consider that the tubercle bacillus

must be strongly suspected of being the infectious organism in all cases of lymphadenitis in the mesentery (Clute; Struthers; Guleke; Bell; McFadden). In fact, the age period in which the disease occurs, the symptomatology, physical findings, laboratory data, etiology, pathology and pathogenic anatomy are so similar that one strongly suspects that the two conditions are simply slight variations of a fundamental disease process.

#### PRIOR INVESTIGATIONS OF MESENTERIC LYMPH NODES

Repeated contact with tuberculous and nontuberculous mesenteric lymphadenitis in the surgical service of the University of Minnesota Hospital led Dr. O. H. Wangensteen to suggest an investigation of the fundamental aspects of the condition. In the preceding survey it is evident that the subject of mesenteric lymphadenitis has evoked considerable clinical interest. Its extent may be measured by the fact that Strömbeck (1932) wrote a monograph of about two hundred and fifty pages regarding a clinical investigation of the condition. He realized, however, the futility of many clinical observations and publications, and thoroughly summed up their deficiencies when he stated: "There are as yet no certain measures of the normal variation of the mesenteric lymph glands. Therefore, the possibility cannot be excluded that in many of the published cases the size of the glands was within normal limits, and that the symptoms were caused by factors which could not be observed objectively." It is this most fundamental factor with which the present study is concerned.

*Historic Data.*—The development of knowledge concerning the lymphatic system has resulted from the studies of widely scattered investigators. The writings of Herophilus are credited with vague references to the lacteal vessels, but the earliest specific knowledge of them was recorded by the Italian, Aselli, in 1627. The Frenchman, Pecquet, in 1651, noticed white fluid in the heart of a dog, and traced it back to the subclavian vein and the thoracic duct. The Swedish investigator, Rudbeck, in 1653, followed the chyle back to the lymph vessels of the mesentery. The Dutchman, Swammerdam, in 1664, discovered the lymphatic valves.

Physiologic studies regarding the lymphatic system progressed more slowly. William and John Hunter, in the eighteenth century, upheld the lymphatic system as the sole absorptive element in the body. Magendie, however, in 1825, showed that the venous radicals were also absorptive structures, and in 1850, Ludwig demonstrated the formation of lymph by the diffusion of fluid from the capillary bed.

Detailed knowledge of the lymph node system has fallen behind that of the lymph vascular system. Bertoin and Worms credited Sydenham with the first description of enlargement of the mesenteric lymph nodes

in children. Monro (1760), however, was the first writer to mention swelling of the lymph nodes in the head, axillae and inguinal regions. Hodgkin is said to have been the first, in 1832, to recognize the possibility of lymph nodes being the seat of specific diseases. Werner and Feller, in 1784, however, described an atrophy and hardening of the mesenteric lymph nodes which they thought to be due to tuberculous.

Knowledge concerning limited portions of the general lymphatic system, such as the lymphatic nodes of the intestinal mesentery, also originated with the early investigators. Aselli found an extensive organization of the mesenteric lymph nodes in dogs. This investigation resulted in the naming of these nodes the pancreas of Aselli.

Mascagni, by 1787, apparently possessed a fairly extensive conception of the mesenteric lymph nodes. He described their shape, and was cognizant of a disease which hardened and atrophied them. He stated that these nodes in children become organized into groups with advancing growth of the body. He believed that the growth of the mesenteric lymph nodes was closely related to the growth of the body, but that in middle life they began to diminish and gradually disappeared.

Cruikshank, in 1786, considered the number of mesenteric nodes to vary from 130 to 150, and he noted a disappearance of some of the nodes in older persons. He stated that they varied in size from  $\frac{1}{20}$  to  $\frac{1}{8}$  inch (0.12 to 0.32 cm.) in diameter. This observation seems to be the first quantitative description of their size. Later writers were more interested in the pathologic conditions affecting the nodes. The only quantitative data recorded by them related to the number of mesenteric lymph nodes.

In 1889, Wullenweber undertook the first quantitative study of the size of mesenteric and mesocolic lymph nodes under normal and pathologic conditions. His method consisted essentially of excision of the nodes and of weighing them in groups of 10, 20 or 50 nodes, from which he obtained an average weight for each of the groups. He did not pretend that his method was particularly accurate, but felt that it offered a better measure of the size of the lymph nodes than had yet been obtained. He found the total number of abdominal lymph nodes to vary from 154 to 540 in a series of seventeen patients ranging in age from birth to 52 years. The variation in weight of these nodes was extreme, ranging from 0.0002 to 3.22 Gm. The mesenteric lymph nodes were examined separately in only four patients, ranging from 11 to 68 years of age. The number in these cases varied from 113 to 437, and the average weight of the lymph nodes varied from a minimal of 0.002 to 3.22 Gm. The average weight of the entire group of mesenteric lymph nodes in these cases varied from 0.025 to 0.044 Gm. He concluded from his study of this group of cases that there was a distinct growth in the lymph nodes of the mesentery and abdomen which paralleled general



bodily development, and that with increasing age after the developmental period a decrease in the size of the nodes takes place. It would seem, however, that the results of this investigation hardly merit such a sweeping conclusion, because of the few cases studied.

*Anatomy.*—The following description by Delamere, Porier and Cuneo shows the regional lymph nodes dealt with in the present investigation:

The lymphatics of the cecum and appendix are much more developed than those of other segments of the intestine. There are a few small nodes on the anterior and posterior surfaces of the cecum which terminate in a fairly large group of nodes (5 or 6) at the termination of the ileocecal artery. The appendical glands are essentially the same group, although there may be interposed in their route a few nodules in the retroileal meso-appendix.

The lymphatics of the small intestine form two systems relatively independent of one another draining the mucosal and muscular layers of the intestinal walls. The glands in the mesentery into which the collecting trunks empty appear at first glance to be scattered indiscriminately through the mesentery. They are, however, arranged in a fairly definite plan and may be divided into three groups. A primary group is present placed in the terminal arterioles arising from the last anastomotic arch. A second group is present in the course of the primary superior mesenteric branches at the level of the first anastomotic arch. These glands are larger than the primary group. A third group may be found around the trunk of the superior mesenteric artery at its commencement. The glands are most numerous in the jejunal mesentery, diminishing progressively in number to the terminal ileum.

#### QUANTITATIVE STUDY OF MESENTERIC NODES

The aim of this investigation has been to determine the normal weight of mesenteric lymph nodes in children. Such a study seemed so beset by uncontrollable factors and inaccuracies of observation that the results would probably be of little value; nevertheless, the entire clinical entity built around apparent enlargement of the mesenteric lymph nodes would remain largely hypothetical unless some determination of the normal was made for purposes of comparison. Consequently, an attempt has been made to establish a concept of the normal size of these nodes. The problem has been attacked without the influence of preconceived ideas, and the many variable factors affecting such an undertaking have been faithfully recorded in order that any reader may judge for himself as to their significance.

*Material.*—It was proposed to study the size of the mesenteric lymph nodes in infants and children from birth to 15 years of age. This period of life was chosen arbitrarily in order that the investigation might be closely linked to the clinical entity of mesenteric lymphadenitis, wherein both the tuberculous and the nontuberculous types are encountered during this age period.

Arrangements were made with the pathology departments of the University of Minnesota, Minnesota General Hospital, Minneapolis General Hospital and Ancker (St. Paul City and County) Hospital, whereby autopsy specimens from children within the desired age group were obtained. The various pathologists and their

assistants in these institutions gave hearty cooperation in the collection of this material.

Specimens chosen for study consisted of mesenteries from premature and full-term stillborn infants, in whose cases there had been no history of recent maternal infection, and in whom the pathologist had found no evidence of a disease process related to the gastro-intestinal tract. Mesenteries fulfilling these requirements were obtained without great difficulty, because of the large number of autopsies performed on stillborn infants in the department of pathology at the University of Minnesota.

Considerable difficulty was encountered, however, in the collection of adequate material during infancy and childhood. Death from accidental causes was thought to preclude to some extent the possibility of recent infections affecting the mesenteric nodes, and consequently the material was limited, at first, to cases in which the cause of death had been accidental. No such cases were obtained, in spite of cooperative pathologists, because apparently children dying from this cause are seldom subjected to a postmortem examination. Furthermore, it was soon evident that there was not only an extreme scarcity of traumatic accident material, but that autopsies on children more than 2 years of age were infrequent.

My views necessarily broadened, and it was felt that specimens from almost any patient dying in childhood would be acceptable except those with diseases of the reticulo-endothelial system. This conversion was influenced by the obvious fact that no mesenteric nodes after birth would be exempt from the effects of organisms or toxins derived from the gastro-intestinal tract. In other words, no absolutely uncontaminated or completely normal lymph node system would be encountered. Furthermore, the effects of the various causes of death on the size of the nodes could not be evaluated, for no normal size of lymph nodes had been determined. It was concluded that the investigation must commence somewhere, and its results evaluated with due regard for many possible influential factors.

The material examined consisted of fifty cases occurring in children aged from 4.5 months prematurity to 12 years (table 2). The study included mesenteries from thirteen premature infants, five full-term infants, ten infants less than 1 month old, ten infants ranging from 1 to 6 months of age, two infants between 6 months and 1 year, three children between 1 and 2 years, one child of 4 years, two children between 5 and 6 years, three children of 8 years and one child 12 years of age. The sex distribution was fairly even, there being twenty-two female and twenty-eight male infants and children examined. The various causes of death included prematurity, anencephaly, cerebral hemorrhage, hydrocephalus and spina bifida, hydrops foetalis, strangulated hernia and peritonitis, congenital heart disease, pneumonia, meningitis, otitis media, mastoiditis, pertussis, intussusception, congenital syphilis, dysentery, abscess of the lungs, septicemia, rectovaginal fistula, pericarditis, third degree burns, rheumatic heart disease, poliomyelitis and abscess of the brain.

*Methods.*—The specimens received from the various pathologists consisted of the entire mesentery of the small intestine extending from the duodenojejunal juncture to the cecum. The mesentery had been cut across at its attachment to the posterior body wall, thus including in each specimen a portion of the superior mesenteric artery proper. The intestinal tract was present in the peripheral margin of the mesentery. The vermiform process and cecum were preserved in each instance, in order that the proximal or distal portions of the mesentery might be more easily identified. All specimens were immediately placed in formaldehyde U. S. P. (1:10), which was the standard fixative solution used in the various hospitals and pathologic laboratories.

TABLE 2.—Summary of Observations on Fifty Subjects

Case	Age*	Sex	Cause of Death	Jejunal Region			Ileal Region			Me-senteric Root Region			Total Mesenteric Lymphoid Tissue		
				No. of Nodes	Average Weight, Gm.	No. of Nodes	Average Weight, Gm.	No. of Nodes	Average Weight, Gm.	No. of Nodes	Average Weight, Gm.	Total Weight, Gm.	No. of Nodes	Average Weight, Gm.	Total Weight, Gm.
1	Prem. 4½ mo.	F	Prematurity.....	27	0.0006	13	0.0007	7	0.0071	47	0.0016	0.0753			
2	Prem. 4½ mo.	F	Prematurity.....	31	0.0005	9	0.0014	8	0.0021	48	0.0009	0.0175			
3	Prem. 6 mo.	M	Prematurity.....	53	0.0017	34	0.0019	20	0.0039	107	0.0023	0.2381			
4	Prem. 7 mo.	F	Prematurity.....	68	0.0062	31	0.0018	10	0.0049	112	0.0107	1.1952			
5	Prem. 7 mo.	F	Prematurity.....	12	0.0020	11	0.0030	9	0.0071	32	0.0039	0.1251			
6	Prem. 7 mo.	F	Prematurity.....	74	0.0001	22	0.0002	11	0.0011	107	0.0002	0.0258			
7	Prem. 7 mo.	F	Prematurity.....	63	0.0008	42	0.0019	29	0.0019	137	0.0033	0.4520			
8	Prem. 7 mo.	F	Prematurity.....	52	0.0009	29	0.0008	9	0.0046	90	0.0017	0.1618			
9	Prem. 7 mo.	F	Prematurity.....	12	0.0014	3	0.0042	11	0.0101	20	0.0019	0.1291			
10	Prem. 8 mo.	M	Prematurity.....	56	0.0004	29	0.0003	16	0.0029	105	0.0008	0.0913			
11	Prem. 8 mo.	F	Anencephalic.....	49	0.0019	20	0.0028	23	0.0112	85	0.0039	0.3393			
12	Prem. 8 mo.	F	Prematurity.....	119	0.0015	53	0.0015	195	0.0076	311	0.0022	0.3577			
13	Prem. 8 mo.	M	Cerebral hemorrhage.....	61	0.0036	20	0.0019	0	0.0000	81	0.0039	0.3207			
14	S. B. F. T.	M	Prematurity.....	37	0.0016	46	0.0036	21	0.0243	104	0.0071	0.7468			
15	S. B. F. T.	M	Splina bilida; hydrocephalus.....	53	0.0048	32	0.0041	28	0.0356	118	0.0126	1.4849			
16	S. B. F. T.	F	Prematurity.....	203	0.0031	75	0.0041	11	0.0204	280	0.0046	2.80			
17	S. B. F. T.	F	Prematurity.....	46	0.0065	50	0.0041	16	0.0218	112	0.0062	0.6986			
18	S. B. F. T.	F	Prematurity.....	28	0.0041	16	0.0041	18	0.0305	62	0.0120	0.8003			
19	1 day	M	Hydrops foetalis.....	33	0.0025	33	0.0036	6	0.0075	72	0.0095	0.1800			
20	7 days	M	Strangulated hernia; peritonitis.....	84	0.0004	33	0.0041	11	0.0188	137	0.0075	0.3199			
21	10 days	M	Congenital heart disease.....	105	0.0061	84	0.0041	26	0.0230	215	0.0171	1.6721			
22	11 days	F	Pneumonia.....	60	0.0049	27	0.0041	9	0.0230	103	0.0171	0.7409			
23	12 days	M	Bronchopneumonia.....	111	0.0021	27	0.0041	10	0.0319	190	0.0171	1.4355			
24	13 days	M	Meningitis.....	30	0.0045	69	0.0041	2	0.1070	40	0.0171	0.7551			
25	13 days	M	Mastoiditis; bronchopneumonia.....	37	0.0103	27	0.0041	16	0.0765	84	0.0171	1.3509			
26	13 days	M	Otitis media.....	78	0.0042	118	0.0041	31	0.0203	264	0.0171	4.50			
27	17 days	F	Pneumonia.....	97	0.0049	63	0.0041	14	0.1551	57	0.0171	2.85			
28	2 mos.	F	Rheumatic heart disease.....	48	0.0057	13	0.0041	10	0.0300	79	0.0171	1.355			
29	3 mos.	M	Mastoiditis; lobar pneumonia.....	42	0.0069	51	0.0041	0	0.0000	61	0.0171	1.047			
30	4 mos.	M	Hydrocephalus.....	43	0.0065	37	0.0041	28	0.0393	104	0.0171	1.357			
31	4½ mos.	M	Congenital heart disease.....	41	0.0065	37	0.0041	10	0.0391	133	0.0171	1.357			
32	5 mos.	M	Otitis media.....	33	0.0065	21	0.0041	22	0.0373	76	0.0171	1.357			
33	5 mos.	F	Intussusception.....	42	0.0182	17	0.0041	17	0.2150	76	0.0171	1.357			
34	6 mos.	F	Dysentery.....	62	0.0129	10	0.0041	15	0.1169	87	0.0171	2.2			
35	9 mos.	F	Congenital syphilis.....	91	0.0048	81	0.0041	37	0.0192	209	0.0171	3.57			
36	11 mos.	F	Meningococcal meningitis.....	29	0.0247	26	0.0041	20	0.1851	75	0.0171	1.357			
37	13 mos.	F	Bronchopneumonia.....	49	0.0139	30	0.0041	15	0.2006	94	0.0171	1.64			
38	13 mos.	F	Abscess of lung.....	65	0.0227	62	0.0041	16	0.0402	143	0.0171	2.47			
39	2 yrs.	F	Septicemia.....	46	0.0177	52	0.0041	11	0.1316	109	0.0171	1.85			
40	4 yrs.	F	Rectovaginal fistula.....	121	0.0177	72	0.0041	33	0.2321	231	0.0171	3.97			
41	5 yrs.	F	Pericarditis.....	59	0.0005	63	0.0041	24	0.1113	146	0.0171	2.47			
42	6 yrs.	F	Third degree burns.....	106	0.0175	104	0.0041	2	0.0635	212	0.0171	3.64			
43	8 yrs.	F	Pneumonia.....	15	0.0841	8	0.0041	34	0.3113	57	0.0171	1.1			
44	8 yrs.	M	Pneumonia endocarditis.....	55	0.0136	45	0.0041	24	0.2782	124	0.0171	2.14			
45	9 yrs.	M	Polymyositis.....	157	0.0167	66	0.0041	39	0.1448	262	0.0171	4.48			
46	12 yrs.	M	Abscess of the brain.....	71	0.0504	32	0.0041	9	0.8409	116	0.0171	1.99			
47		M		91	0.0321	40	0.0041	8	0.6504	139	0.0171	2.37			

\* Prem. means premature, S. B., stillborn, and F. T., full-term.

The effect of formaldehyde in various strengths on the mesenteric lymphoid tissues was carefully considered. Six lymph nodes from the mesentery of a still-born full-term infant were dissected free and weighed individually. Two of these nodes were then placed in a 5 per cent solution of formaldehyde, 2 in a 10 per cent solution and 2 in a 15 per cent solution. The weight of the nodes in each solution was then recorded daily for a time, later it was recorded every other day, and as soon as the change in weight became less rapid records were made at weekly intervals. These observations showed an immediate increase in the weight of the nodes, the greatest increase taking place in the nodes placed in the 5 per cent solution and the least increase in the lymphoid tissue placed in the 15 per cent solution (table 3). The rapid increase in weight was followed by a fairly rapid and steady decrease in the weight of the nodes in each fixative solution. Finally, the loss of weight ceased, and it was noted that the lymphoid tissue

TABLE 3.—Changes in Weight of Mesenteric Lymph Nodes During Fixation (Gm.)

Date	5% Formaldehyde		10% Formaldehyde		15% Formaldehyde	
	A	B	C	D	E	F
2/25/31.....	0.2364	0.2327	0.1874	0.1931	0.1542	0.1262
2/26/31.....	0.2360	0.2330	0.1950	0.1965	0.1556	0.1294
2/27/31.....	0.2341	0.2324	0.1946	0.1962	0.1541	0.1284
2/28/31.....	0.2324	0.2319	0.1901	0.1910	0.1522	0.1267
3/ 1/31.....	0.2308	0.2310	0.1850	0.1880	0.1500	0.1234
3/ 2/31.....	0.2296	0.2484	0.1872	0.1864	0.1398	0.1209
3/ 3/31.....	0.2274	0.2461	0.1857	0.1869	0.1399	0.1287
3/ 4/31.....	0.2269	0.2460	0.1842	0.1871	0.1500	0.1277
3/ 5/31.....	0.2266	0.2454	0.1856	0.1870	0.1492	0.1261
3/ 6/31.....	0.2251	0.2447	0.1824	0.1864	0.1472	0.1250
3/ 7/31.....	0.2244	0.2449	0.1810	0.1845	0.1451	0.1217
3/ 8/31.....	0.2230	0.2440	0.1781	0.1796	0.1429	0.1244
3/10/31.....	0.2227	0.2438	0.1769	0.1745	0.1417	0.1241
3/12/31.....	0.2222	0.2435	0.1751	0.1740	0.1416	0.1241
3/14/31.....	0.2216	0.2432	0.1739	0.1738	0.1414	0.1210
3/16/31.....	0.2212	0.2425	0.1722	0.1731	0.1411	0.1237
3/18/31.....	0.2209	0.2426	0.1704	0.1714	0.1409	0.1239
3/20/31.....	0.2206	0.2421	0.1678	0.1709	0.1409	0.1237
3/27/31.....	0.2205	0.2420	0.1641	0.1696	0.1408	0.1234
4/ 3/31.....	0.2202	0.2419	0.1620	0.1662	0.1407	0.1232
4/10/31.....	0.2200	0.2416	0.1600	0.1650	0.1407	0.1231
4/17/31.....	0.2200	0.2415	0.1590	0.1651	0.1407	0.1230
4/24/31.....	0.2200	0.2416	0.1590	0.1650	0.1407	0.1231
Weights Unfixed, Gm.						
2/23/31.....	0.1700	0.1801	0.1590	0.1650	0.1350	0.1172

placed in the 10 per cent solution of formaldehyde had returned to its original weight. The specimens of tissue placed in the 5 and 15 per cent solution failed to return to their original weights. The 10 per cent solution of formaldehyde, therefore, was concluded to be the most desirable fixative, as no corrective factor need be used. The mesenteric lymph node tissue returned to its original nonfixed weight after a period of approximately two months, following which there was no appreciable change in weight. Consequently, all specimens were fixed in a 10 per cent solution of formaldehyde for a period of 2.5 months before being studied.

The individual lymph nodes were dissected free from the mesenteric fat, areolar tissue and peritoneum with sharp dissecting scissors. The smallest mesenteric nodes (0.0001 Gm.) could be seen with the naked eye if the mesentery was held up to a strong light and transilluminated. The dissections were made easier by using an ophthalmologic loupe, by means of which the details of the tissue were magnified and consequently better visualized. Dissection of nodes of all sizes showed that they could easily be freed from the surrounding tissues. Fixation of the tissues in a solution of formaldehyde seemed to give the lymph nodes a

quality of firmness which considerably facilitated their dissection, for earlier dissection of the tissues in the fresh unfixed specimen was very unsatisfactory.

It was felt that some question might arise as to whether the extremely small bits of tissue described as lymph nodes might not be simply small collections of fat in the mesentery. Furthermore, the adequacy of the dissection with regard to stripping the node free from adherent tissues might be questioned, as even a small amount of tissue left clinging to such a small object would affect its weight value tremendously. Therefore, nodes of variable size were picked at random during

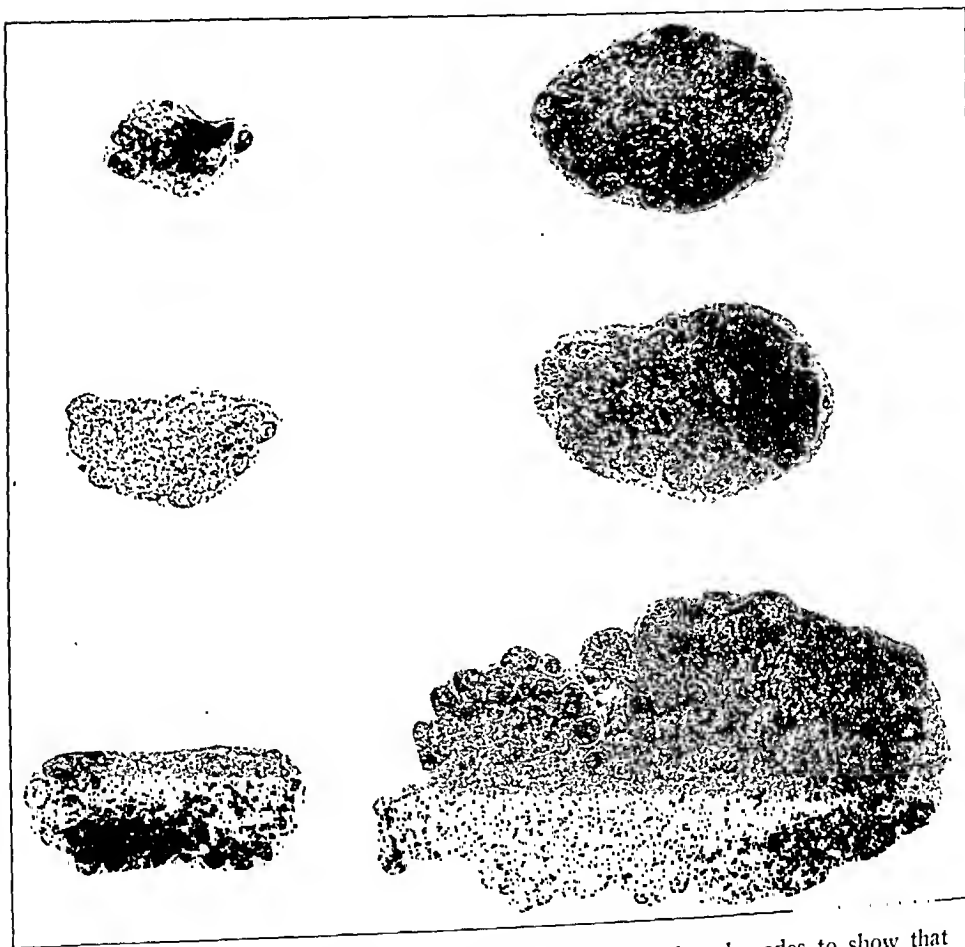


Fig. 5.—Photomicrographs of a series of mesenteric lymph nodes to show that the small bits of dissected material are lymphoid structures and to show how little adherent extraneous tissue is present following careful dissection. The nodes vary in weight from 0.0001 to 0.5 Gm.;  $\times 8$ .

the dissections, and after their weights had been recorded in the usual fashion, microscopic sections were made. Figure 5 shows this series of nodes, which vary in weight from 0.0001 to 0.5 Gm., and demonstrates clearly that the tissue is lymphoid and that the nodes have been dissected free down to the capsule, with practically no adherent extraneous tissue.

The mesentery was replaced in the fixative solution after the dissection of each node had been completed, and the free node was dried before being weighed. The

drying process consisted of removing any apparent excess fluid that might be present by gently rolling the node over absorbent paper.

The lymph node was then weighed on a chemical balance. A question immediately arose as to the advisability of single or multiple observations on weight. Consequently, a series of lymph nodes were weighed once and the single result recorded. Again, each node was weighed five times, and an average of each series of weight tabulations was computed. It appeared from this study that the initial weight was as accurate as an average based upon five records. Therefore, all the weights recorded in this article represent single determinations.

Each lymph node was treated in this way as an individual problem. The mesentery was first transilluminated; the lymph node was then carefully dissected

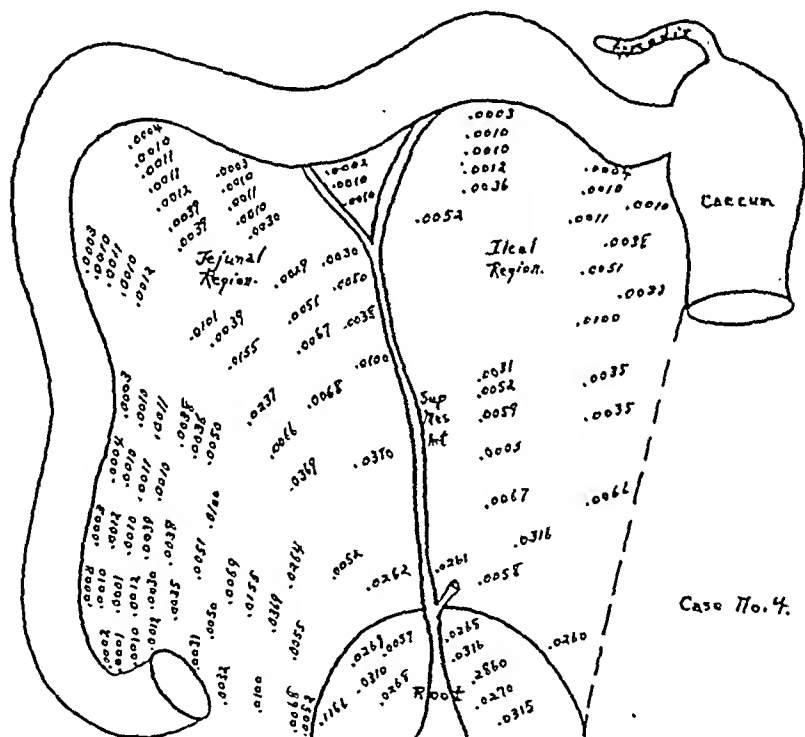


Fig. 6.—The original charts on which the weight of each lymph node was recorded in the approximate position in which it was found in the respective mesentery. The charts are organized in age sequence and labeled with the case number. The portions of the intestinal tract which were attached to the mesentery and the arbitrary regions of dissection are indicated.

free; it was dried on absorbent paper and weighed. This process was carried out on 6,008 individual lymph nodes which were encountered in the fifty specimens studied.

It was felt that each observation should be recorded as accurately as possible in order that any obscure but significant factors might not be overlooked. Consequently, an outline of the mesentery was drawn for each specimen, and the determinations of weight were recorded on the sketch in as near the same position as each node was found in the specimen. Figure 6 illustrates this method of recording the original observations.<sup>1</sup>

1. Reproduction of the recorded observations on the other forty-nine specimens has been omitted because of lack of space.

*Observations.*—Transillumination of the mesenteries of several specimens before commencing dissections indicated an apparent gradation of size of the nodes in various regions. The nodes along the intestinal margin of the mesentery, for instance, appeared to be the smallest, and those at the root of the mesentery appeared to be the largest. Therefore, an area arbitrarily marked off as the root region was indicated on the record chart of each specimen. Furthermore, examination of the record charts after a few dissections had been completed revealed a slight suggestion of greater weight of the nodes in the region of the ileum and ileocecal junction than in the region of the duodenojejunal junction and jejunum. The central branch of the superior mesenteric artery, as it coursed through the mesentery, was indicated in each chart as an arbitrary division line between the jejunal and the ileal regions.

Inspection of the reproduction of the charts (fig. 6) on which the original observations were recorded shows clearly how most of the smallest lymph nodes were consistently present in the periphery or intestinal margin of the mesentery. However, a comparison of the average weights of lymph nodes of the jejunal and ileal regions (table 2) fails to confirm the impression that nodes are larger in the ileal region. This observation seems to be of significance in view of the descriptions of the mesenteric lymph nodes by older writers in which it was repeatedly stated that the largest lymph nodes are encountered along the largest blood vessels, most of which are in the ileal region. The latter region contains the largest branches of the superior mesenteric artery, and yet the average weight of the lymph nodes in that region does not seem to vary significantly from the average weight of the nodes in the jejunal region. It is clear from table 2, however, that the average weight of the lymph nodes of the root region far exceeds that of those of both the jejunal and the ileal regions.

The weights of the respective nodes were mentally gaged during the course of the dissections. Thus, an attempt was made to guess with fair accuracy whether one node was larger than another. Furthermore, the nodes were inspected for possible correlation between the apparent size of the nodes and the actual size, as determined by their respective weights. It was observed during the entire course of the dissections that there was a close correlation between the actual weight of a node and the visual impression of its size. Thus, a small node generally weighed less than a large node, and there was apparently little deviation in the density of the tissue involved which might make a small compact node as heavy as a large loosely woven node. In other words, the apparent size of the node was indicative of its weight.

This observation seemed to be of some importance from a clinical point of view, for if a surgeon has a fairly accurate concept of the normal size of lymph nodes in the mesentery, his recognition and evaluation of the size of nodes in pathologic conditions of the mesentery should be of definite significance. Thus, it would seem safe to decide that descriptions of enlargement of the mesenteric nodes by surgeons familiar with the usual appearance of the mesentery are in all probability correct. In order to test this observation further six cases were chosen at random after the dissections had been completed. The dissected nodes in each case were then examined, and 4 nodes were chosen; a very small one, a large one and 2 of intermediate size. They were

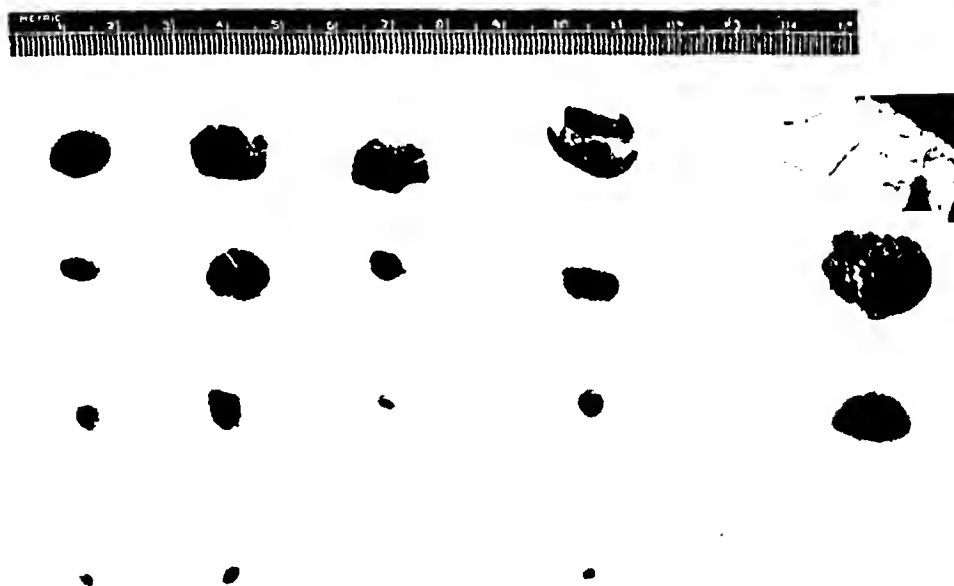


Fig. 7.—Nodes chosen by inspection, in which there is an apparent variation in size. The smallest nodes actually weigh the least and the largest nodes weigh the most.

then weighed to determine whether or not there was a correlation between their observed size and their actual weight. In each instance the apparently smallest node weighed the least, and the actual weight of each node became greater with an increase in the gross size (fig. 7). This test would seem to lend credence to descriptions of enlarged mesenteric nodes by clinical observers.

#### TREATMENT OF DATA

Data derived from individual examination of 6,008 mesenteric lymph nodes were first recorded on the fifty case charts. The material was



then organized as shown in table 2 according to age, sex, cause of death, number of lymph nodes and weight of the tissue, in order to facilitate a more panoramic study, which might suggest certain conclusions.

The cases were listed in age sequence from birth to 12 years according to the total number of lymph nodes, the total weight and the average weight of the lymph nodes. Furthermore, the number of lymph nodes and the average weight of the nodes for the jejunal, ileal and root regions were recorded.

Inspection of the tabulation shows a marked preponderance of new-born infants. The reasons for this imbalance of specimens according to age have already been given. There was considerable variation in the number of lymph nodes, and it is interesting to note that both the smallest and the largest number of nodes were encountered in the group of new-born infants. The number of nodes varied from 26 in a 7 month premature infant to 289 in a full-term stillborn infant.

The total amount of lymphoid tissue present in each mesentery varied from 0.0298 Gm. in a 6 month premature infant to 18.654 Gm. in an 8 year old child. The average weight of the lymph nodes for each mesentery varied from 0.0002 Gm. in a 7 month premature infant to 0.2095 Gm. in a 6 year old child. The smallest node encountered in the dissections weighed 0.0001 Gm. and the largest weighed 1.78 Gm. There was an apparent steady increase in the total weight of the lymphoid tissue of the mesenteries from birth to 12 years of age. The average weight of the lymph nodes followed this general trend closely. Furthermore, the average weight of the nodes of the arbitrarily designated jejunal, ileal and root regions seemed to follow the same trend.

Graphic analysis of the data was then carried out in order to verify or negate those impressions (fig. 8). The average weights of the lymph nodes in the specified regions and the average weight of the nodes for each complete mesentery were plotted against the age in years. The jejunal and ileal regions in each case, as well as the average weight of the lymph nodes derived from the total lymphoid tissue in the mesentery are represented in centigrams. It was necessary to plot the average weights of the root region in decigrams because of the larger numerical values encountered.

Each graph emphasizes the larger number of cases in the group of the new-born and the rapidly diminishing number with increase in age. There is a definite verification of the impression, gained from an inspection of table 2, that the average weight of the mesenteric lymph nodes increases with age. Graphic analysis of the various arbitrarily demarcated regions of the mesentery indicates that all follow the same trend.

A marked deviation from the steady increase in weight with age is noted between the ages of 8 and 12 years. The significance of this is conjectural, as only one case of a 12 year old subject was available. Consequently, the variance from the general trend might well be due to an inadequate number of cases. The fact that the weight of the nodes at the mesenteric root in this case continued to become greater somewhat substantiates this possibility. Further comment, such as argumentation favoring a peak of growth at about 12 years of age with gradual recession of the lymphoid tissue, is not necessary because of the minimal amount of available material studied during this age period.

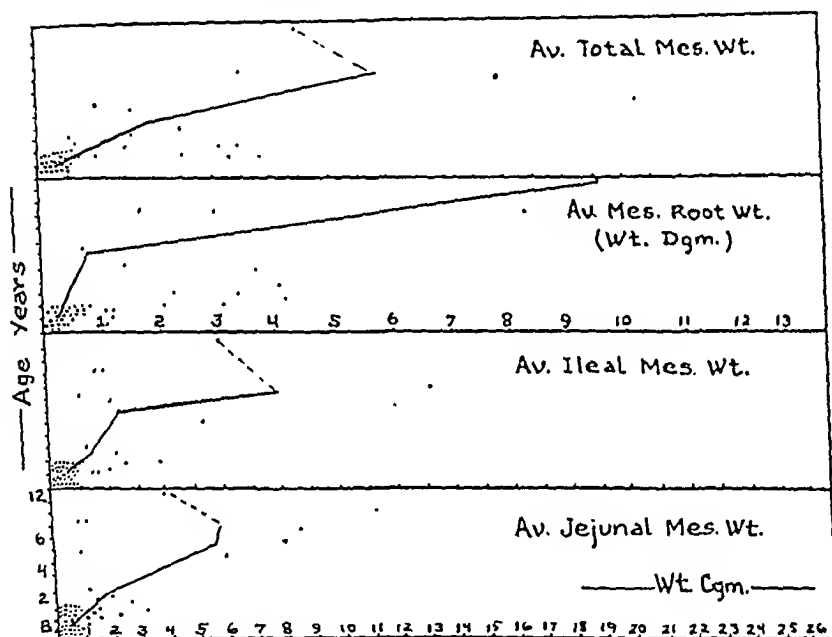


Fig. 8.—A graphic analysis of the average weights of the lymph nodes of the mesentery and its arbitrarily demarcated regions. The weights for the mesentery as a whole and for the ileal and jejunal regions are recorded in centigrams. Those for the root region are recorded in decigrams, because of the large numerical values encountered. The ages are recorded in years. The dotted portions of the curves indicate the deviation from the steadily ascending line to the single case in a 12 year old child.

Examination of the tabulated figures for the jejunal, ileal and root regions reveals an apparent increase in the average weight of their nodes. For example, the smallest average weight of nodes in the jejunal region was found to be 0.0001 Gm. in a 7 month premature infant; the largest was 0.0904 Gm. in an 8 year old child. The smallest and largest average weights in the ileum of the same cases varied from 0.0002 Gm. to 0.1297 Gm., respectively. The smallest average weight

in the root region was encountered in the same 7 month premature infant, 0.0011 Gm., and the largest was found to be 0.9564 Gm. in a 12 year old child.

The manifest difference in the average weight of the lymph nodes of the arbitrary regions of the mesentery with a progression from jejunum to ileum to root suggested a statistical analysis of available data.<sup>1</sup> The mean of the number of lymph nodes and the mean of the average weights of the nodes for the three regions were established. The standard deviation and the standard error of the means were calculated. Comparisons were made as recorded in table 4. A significant difference between the number of nodes in the jejunal and ileal, the

TABLE 4.—*Comparison of Means for Number of Nodes and Their Average Weights in the Jejunal, Ileal and Root Regions*

Regions		Difference of Mean	Standard Error of Difference	Ratio	Probability
Number of Nodes					
Jejunum (Mj $\pm$ S.E.) 63.56 $\pm$ 2.72	Ileum (Mi $\pm$ S.E.) 39.82 $\pm$ 3.7942	23.74	4.66	5.094	0.000,000,6
Jejunum (Mj $\pm$ S.E.) 63.56 $\pm$ 2.72	Root (Mr $\pm$ S.E.) 16.78 $\pm$ 8.3714	46.78	8.802	5.314	0.000,000,04
Ileum (Mi $\pm$ S.E.) 39.82 $\pm$ 3.7942	Root (Mr $\pm$ S.E.) 16.78 $\pm$ 8.3714	23.04	9.190	2.507	0.012
Average Weights					
Jejunum (Mj $\pm$ S.E.) 0.0122 $\pm$ 0.0029	Ileum (Mi $\pm$ S.E.) 0.0127 $\pm$ 0.0028	-0.0005	0.00403	-0.125	0
Jejunum (Mj $\pm$ S.E.) 0.0122 $\pm$ 0.0029	Root (Mr $\pm$ S.E.) 0.0962 $\pm$ 0.0258	-0.0840	0.0259	-3.2432	0.0014
Ileum (Mi $\pm$ S.E.) 0.0127 $\pm$ 0.0028	Root (Mr $\pm$ S.E.) 0.0962 $\pm$ 0.0258	-0.0835	0.0259	-3.223	0.0014

jejunal and root and the ileal and root regions is demonstrated by these comparisons. There is, however, no real difference between the average weight of the nodes in the jejunal and ileal regions. Comparisons of the average weights of the lymph nodes of the jejunal and root and the ileal and root regions show a decided difference.

1. These calculations were made in the following manner:

$$\text{Mean} = \sqrt{1x} = \frac{\sum x}{n}$$

$$\sqrt{2x} = \frac{\sum x^2}{n}$$

$$n2x = \sqrt{2x} = (\sqrt{1x})^2$$

$$\text{Standard deviation of the mean} = \sigma x = \sqrt{n2x}$$

$$\text{Standard error of the mean} = \text{S.E.}_m = \frac{\sigma x}{\sqrt{n-1}}$$

## COMMENT

The clinical aspects of mesenteric lymphadenitis have been dealt with in considerable detail. Many points of similarity between the tuberculous and nontuberculous types have been pointed out. Possibilities for confusion of the two entities have been shown to be present, especially in the early manifestations of the disease process. Their individuality, however, depends more on the fact that the etiologic agents are different than on divergent symptomatology. Thus, the reaction of the human organism to tuberculous and pyogenic invasion of the mesenteric lymph nodes is much the same. Yet the impression is gained that the tuberculous type progresses steadily to calcification, or the end-stage of tuberculous infection, while the pyogenic type is transient and self-limited. The two types of etiologic agents in all probability gain access to the mesenteric lymph nodes in the same fashion, the reaction of the body and the local nodes being essentially the same as in infections in other locations. It is generally accepted that the cervical and inguinal lymph nodes may be enlarged following either tuberculous or nontuberculous infections of the regions drained by them. There is every reason to expect that the mesenteric lymph nodes react to infection of the regions drained by them in much the same fashion. It is therefore concluded that tuberculous and nontuberculous mesenteric lymphadenitis are separate clinical entities.

The treatment of enlargement of the mesenteric nodes has been surgical or supportive. No mention has been noted, in the considerable surgical literature relative to tuberculous mesenteric lymphadenitis, regarding the use of roentgen therapy. Yet the treatment is well known and accepted in tuberculosis of the cervical and inguinal lymph nodes, for it was one of the first conditions to be treated successfully with roentgen rays. The earliest reports regarding the use of roentgen rays in the treatment of cervical tuberculous adenitis were made in this country in 1903 by Williams, Varney and others, and in recent years the literature on the subject has become voluminous. Good articles, many of which contain excellent illustrations and careful technical descriptions, have been published by Weil, Boggs and others. MacKee stated that while there are no available comparative statistics, it is the prevailing opinion that irradiation together with general medical treatment is more successful in a majority of cases of severe local tuberculous cervical adenitis than is surgery, in point of clinical cure, permanent cure, discomfort and disfigurement. Radium has not yet been employed extensively in the treatment of tuberculous adenitis. The literature contains few reports of such treatment. Molyneux reported the successful treatment of thirty patients with radium without radium sequelae. Therapeutic results are considered to be the same with both agents. Roentgen ray treatment of tuberculous adenitis has been used with

brilliant results in Germany and has been applied by roentgenologists to tuberculous mesenteric lymphadenitis (Müller). The treatment of this condition has been successful, and has been recommended (Birk and Schall). The technic is essentially the same as for treatment of tuberculous peritonitis.

It is clear that this study has embraced only a small segment of a great problem, in which one portion at a time must be completed before a comprehensive picture may be formed. The original hope of establishing a definite concept of the normal size of the mesenteric lymph nodes has been only partially realized. The incomplete solution of the problem has been due to the many uncontrollable factors affecting such an investigation, the most important of which has been the lack of suitable material. The impossibility of obtaining absolutely normal specimens has been pointed out. Yet it would seem that even this complicating factor does not completely disqualify conclusions that may be drawn. This reaction is based on the obvious fact that all other studies of such a nature have been affected by similar uncontrollable factors, and that consequently this study may justly be correlated with them.

Analysis of the data collected by the status lymphaticus investigation committee (Young and Turnbull) supports this contention. The report discussed the size of lymphoid structures, such as the faucial tonsil, cervical lymph glands, mesenteric lymph glands and Peyer's patches in children ranging in age from birth to 16 years. The causes of death are segregated into a so-called normal group, which includes accidents, burns, hemorrhage, poisoning, epilepsy, foreign bodies, drowning and the like, and an abnormal group comprising pneumonia, gastro-enteritis, intussusception, volvulus, intestinal obstruction, appendicitis, meningitis, peritonitis, septicemia, congenital heart disease and the like. The report concluded that comparison of the normal with the abnormal values shows no evidence that the amount of lymphoid tissue is influenced in a special manner by diseases of the type described. Hellman and White and Hammar noted in various illnesses and general infections that the lymph nodes remain essentially unchanged, and that local conditions do not affect the entire lymphoid structure. They expressed the belief that the reaction of the lymphoid tissues to infection is late, and that it proceeds parallel to the formation of antibodies.

Such evidence, indicating that the common acute and subacute pathologic processes occurring in children do not affect the size of the nodes, is presented merely to show that similar investigations are not free from this complicating factor.

The investigation has been somewhat curtailed owing to the scarcity of material between 8 and 15 years of age. Nevertheless it is evident from an inspection of table 2 and figure 16 that there is a fairly steady increase in the average mesenteric weight of the lymph nodes with

advancing age and development of the body. The graphic illustration (fig. 16) of the steady rise in weight of the lymph nodes associated with an increase in age partially confirms the lymphoid type of growth curve recorded by Scammon, for there is a rapid rise in infancy and childhood and a more gradual rise toward puberty. The remaining portion of the growth curve has not been completed, for the study has not as yet been extended beyond the age of adolescence.

The effect of malnutrition or inanition on the weight of the nodes must be considered in a study of this nature. It should be remembered that inanition in these cases is usually secondary to an acute or subacute infectious process which has finally caused death. Some idea of its effects may be gained from studies regarding changes in the weight of the thymus gland during health and disease, for in early life this organ is extremely active in the reticulo-endothelial system. Boyd showed conclusively that there is a distinct loss of weight in this organ when illness has lasted more than twenty-four hours. According to Jackson, lymphoid structures such as the mesenteric nodes undergo atrophy with inanition. It is usually agreed that the condition follows closely on illness in children, and consequently one would expect the nodes in all cases with acute or subacute disease processes to be somewhat atrophic. Jackson, however, pointed out that infection involving the local nodes usually causes them to become engorged and swollen. Prolonged illness without involvement of the local mesenteric nodes and infectious processes definitely affecting them are recorded in table 2 as causes of death. The purpose of this discussion is not to evaluate the effects of the disease processes on the mesenteric nodes, but simply to point them out as uncontrollable factors affecting the study.

The study does not intend to stress the topography of the mesentery and its lymph nodes. Yet incidental knowledge has been obtained which includes verification of data regarding the location of lymph nodes in the mesentery. The older writers (Mascagni and Cruikshank) described the variation in the number of nodes and the fact that the smaller nodes seemed to be in the periphery of the mesentery while the larger ones adhered to the major blood vessels. Those observations are corroborated in this study. Additional information has been gained, however, for the root region has been established as the location of the largest mesenteric nodes.

The conclusions of earlier investigators that there is an increase in the size of the nodes with advancing age through adolescence have been confirmed. Furthermore, the impression that under certain conditions the mesenteric lymph nodes are probably enlarged has been partially substantiated, for it has been demonstrated that more confidence may now be placed in clinical observations. In other words, it has been shown that visual impressions relative to the size of nodes are fairly accurate.

I hope that the data recorded herein may be of value in further similar studies, although the initial aim of the investigation has not been completely fulfilled. The broad field for further similar investigation is manifest.

#### SUMMARY AND CONCLUSIONS

1. A detailed review of tuberculous and nontuberculous mesenteric lymphadenitis shows that the two entities are closely allied and suggests that they may be slightly divergent manifestations of a fundamental disease process.
2. It is concluded that tuberculous and nontuberculous mesenteric lymphadenitis are separate clinical entities.
3. The use of roentgen ray therapy for tuberculous mesenteric lymphadenitis is suggested.
4. No absolutely normal mesenteric lymph nodes are available for study, except those of stillborn infants.
5. Lymphoid tissue placed in formaldehyde, U.S.P. (1:10), returns to its prefixed weight after two months.
6. Lymph nodes weighing as little as 0.0001 Gm. can be dissected free from the mesentery without the adherence of other tissues.
7. The smallest lymph nodes are located near the intestinal margin of the mesentery; the largest are in the mesenteric root.
8. There is a fairly steady increase in the average weight of the nodes from birth to 12 years of age.
9. There is a significant difference between the number of nodes in the jejunal, ileal and root regions of the mesentery.
10. There is no significant difference between the average weights of the nodes of the jejunum and ileum. There is a real difference between the average weights of the nodes of the jejunal and ileal regions and the root region.
11. Visual differentiation is accurate, for the apparent size of a node is fairly indicative of its weight.
12. The effects of infection and inanition cannot be evaluated accurately in a study of this nature. They do not condemn the conclusions just mentioned, for they are present in all similar data.

#### BIBLIOGRAPHY

- Andersen: Universel mesenterial lymfadenit med appendicitlignende sygdomsbillede. Förh. v. nord. kirurg. fören. möde i Islo, 1919, p. 60; also Med. rev. Bergen 36:528, 1919; quoted by Strömbeck.
- Aselli, G.: De lactibus sur lacteis venis, dissert., Milan, 1627; quoted by Garrison.
- Auchincloss, H.: A Clinical Study of Calcified Nodes in the Mesentery, Ann. Surg. 91:401, 1930.

- Bagg, K.: Die "Appendicitisähnliche" isolierte Mesenterialdrüsentuberkulose und ihr Schicksal im weiteren Verlaufe, *Beitr. z. klin. Chir.* **141**:23, 1927.
- Ball, G.: *De tabe mesenterica*, Edinburgh, Baillour and Snellie, 1773; quoted by Strömbeck.
- Bartel, J.: Zur Frage der Latenz der Tuberkulose, *Wien. klin. Wchnschr.* **18**:241, 1905.
- Bell, L. P.: Mesenteric Lymphadenitis Simulating an Acute Abdominal Condition, *Surg., Gynec. & Obst.* **45**:465, 1927.
- Bertein and Worms: Les adénopathies du mésentère, *Gaz. d. hôp.* **82**:1,291, 1909; quoted by Strömbeck and others.
- Bier, A.: Fünf interessante Bauchoperationen, *Deutsche med. Wchnschr.* **18**:538, 1892.
- Birk, W., and Schall, L.: *Lehrbuch der Strahlentherapie*, Berlin, Urban & Schwarzenberg, 1926, vol. 3, p. 713.
- Boggs, R. H.: Tuberculous Adenitis and Its Treatment by Roentgenotherapy, *Am. J. Roentgenol.* **5**:425, 1918.
- Boyd, E.: The Weight of the Thymus Gland in Health and in Disease, *Am. J. Dis. Child.* **43**:1162 (May) 1932.
- Braithwaite, L. R.: Tuberculosis of Glands in the Ileo-Caecal Angle: A Cause of Pain in the Right Iliac Fossa, *Brit. J. Surg.* **13**:439 (Jan.) 1926.
- Branson, W. P. S.: Abdominal Tuberculosis in Childhood: A Clinical Study, *Med.-Chir. Tr., London* **88**:349, 1903.
- Brentano: Mesenterialdrüsentuberkulose, *Zentralbl. f. Chir.* **52**:126, 1925.
- Brüning, F.: Akuter Ileus als erstes Krankheits-symptom der Dünndarmtuberkulose und Bemerkungen über die Tuberkulose der Mesenterialdrüsen, *Deutsche med. Wchnschr.* **45**:1105, 1919.
- Carr, J. W.: The Starting Point of Tuberculous Disease in Children, *Tr. M. Soc. London* **17**:288, 1894.
- Carson, H. W.: The Clinical Aspects of Tuberculous Mesenteric Glands, *Lancet* **1**:259, 1918.
- Clute, H. M.: Enlarged Mesenteric Lymph Nodes, *Boston M. & S. J.* **163**:469, 1920.
- Colman, W. S.: The Distribution of Tubercle in Abdominal Tuberculosis, *Brit. M. J.* **2**:740, 1893.
- Conrath, V.: Ueber die lokale chronische Caecumtuberkulose und ihre chirurgische Behandlung, *Beitr. z. klin. Chir.* **21**:1, 1898.
- Corner, E. M.: The Surgical Treatment of Tuberculous Glands in the Mesentery, *Lancet* **2**:1825, 1905.
- Surgical Treatment of Tuberculous Glands in the Mesentery, *Brit. M. J.* **2**:913, 1908.
- Tuberculosis of the Mesenteric Lymph Glands in Children: Its Nature and Treatment, *Lancet* **1**:426, 1912.
- Cruikshank, W. C.: *Anatomie des vaisseaux absorbants du corps humain*, Paris, Froullé, 1786; quoted by Garrison and Wullenweber.
- Davidovitch, S.: Contribution à l'étude de la tuberculose des ganglions mésentériques, *Presse méd.* **34**:1161, 1926.
- Delamere, G.; Porier, P., and Cuneo, B.: *The Lymphatics*, Chicago, W. T. Keener & Co., 1904.
- Edén, E.: Ett egendomligt fall av tuberkulös peritonit, *Upsala läkeref. förh.* **18**:157, 1913.
- Eisenhart: Ueber Häufigkeit und Vorkommen der Darmtuberkulose, *Inaug. Dissert., Munich*, 1890; quoted by Conrath.



- Fischmann, J.: Arrosion eines Astes der Arteria mesenterica superior infolge von Mesenterialdrüsentuberkulose; Verblutung, Deutsche Ztschr. f. Chir. **233**:73, 1931.
- Floderus: Ueber die primäre Mesenterialdrüsentuberkulose aus chirurgischem Gesichtspunkte, Nord. med. ark. **45**:1, 1912; quoted by Strömbeck.
- Fordyce, A. D.: Dyspepsia and Early Tuberculosis, Brit. M. J. **2**:1751, 1909.
- Franke, E.: Die primäre Mesenterialdrüsentuberkulose und ihre chirurgische Behandlung, Verhandl. d. deutsch. Gesellsch. f. Chir. **43**:258, 1914.
- Freeman, L.: Surgical Significance of Mesenteric Lymphadenitis, Surg., Gynec. & Obst. **37**:149, 1923.
- Garrison, F. H.: History of Medicine, Philadelphia, W. B. Saunders Company, 1929.
- Gehrels, E.: Die chirurgische Mesenterialdrüsentuberkulose, Ergebn. d. Chir. u. Orthop. **12**:333, 1920.
- Golden, R., and Reeves, R. J.: The Significance of Calcified Abdominal Lymph Nodes, Am. J. Roentgenol. **22**:305, 1909.
- Gray, H. F.: Remarks on Obscure Intestinal Colic, Brit. M. J. **1**:253, 1922.
- Grimm, H.: Eine seltene Komplikation der Mesenterialdrüsentuberkulose, Beitr. z. klin. Chir. **141**:718, 1927.
- Guleke: Die Hyperplasie der Mesenterial-Lymphdrüsen, Arch. f. klin. Chir. **133**:517, 1924; quoted by Strömbeck.
- Gutzeit, R.: Strangulationsileus durch eine verkäste Mesenterialdrüse, Zentralbl. f. Chir. **54**:3277, 1927.
- Haman: Statistic der Tuberkulose im Alter von 16-90 Jahren, Inaug. Dissert., Kiel, 1890; quoted by Conrath.
- Hammar, J. A.: Zur Frage der Thymusfunktion, Ztschr. f. mikr.-anat. Forsch. **25**:97, 1931.
- Head, J. R.: Tuberculosis of the Mesenteric Lymph Glands, Ann. Surg. **83**:622, 1926.
- Hellman, T. J., and White, G.: Das Verhalten des lymphatischen Gewebes während eines Immunisierungsprozesses, Virchows Arch. f. path. Anat. **278**:221, 1930.
- Hepburn, T. N.: Tuberculosis of the Mesenteric Lymph Glands as a Cause of Ureteral Obstruction, J. Urol. **2**:385, 1918.
- Heusser, H.: Die Schwellung der mesenterialen Lymphdrüsen, Beitr. z. klin. Chir. **130**:85, 1923.
- Hodgkin, T.: On Some Morbid Appearances of the Absorbent Glands and Spleen, Tr. Med.-Chir. Soc., London **17**:68, 1832.
- Homuth, O.: Akuter Dünndarmileus als erstes Krankheitssymptom bei Mesenterialdrüsentuberkulose geheilt durch Enteroplastik, Deutsche med. Wchnschr. **47**:777, 1921.
- Hubrich, R.: Ein weiterer Fall von Strangulationsileus durch Lymphadenitis mesaraica tuberculosa, Zentralbl. f. Chir. **57**:1856, 1930.
- Iselin, H.: Durchbruch der vereiterten tuberkulösen und mischinfizierten Mesenterialdrüsen, Cor.-Bl. f. schweiz. Aerzte **48**:1569, 1918.
- Jackson, C. M.: The Effects of Inanition and Malnutrition upon Growth and Structure, Philadelphia, P. Blakiston's Son & Company, 1925.
- Jean, G.: Ictères chroniques par tuberculose des ganglions du pédicule hépatique, Presse méd. **33**:38, 1925.
- Jones, A. T.: Tuberculous Glands of the Mesentery, Am. J. Obst. **75**:417, 1917.
- Kappis, M.: Die Sensibilität der Bauchhöhle, Klin. Wchnschr. **4**:2041, 1925.

- Keppler, W., and Erkes, F.: Diagnostische Irrtümer bei Mesenterialdrüsentuberkulose unter besonderer Berücksichtigung der Appendicitis, *Med. Klin.* **15**:301, 1919.
- Koschucharoff, J.: Strangulationsileus durch eine verkäste Mesenterialdrüse, *Zentralbl. f. Chir.* **55**:1846, 1928.
- Krogsgaard, H. R.: Appendicitis lignende mesenterialglandeltuberkulose, *Ugesk. f. læger* **84**:1579, 1922.
- Lennander and Nyström: Kasnistische Beiträge zur Kenntnis der von Enteritis ausgegangenen Peritonitis, *Ztschr. i. klin. Med.* **63**:236, 1907.
- Ljunggren, C. A.: Mesenterialkörteltuberkulosens förekomst hos skolbarn, *Svenska läk.-tidning.* **23**:1107, 1926; quoted by Strömbeck.
- Löwenstein, E.: Die klinische Bedeutung der Tuberkelbazillämie, *München. med. Wchnschr.* **77**:1662, 1930.
- Das Vorkommen der Tuberkelbazillämie bei verschiedenen Krankheiten, *ibid.* **78**:261, 1931.
- Ludwig, C., and Noll, F. W.: *Ztschr. f. rat. Med.* **9**:52, 1850; quoted by Garrison.
- Lund, F. B.: Tuberculosis of the Mesenteric Glands Simulating Appendicitis, *Boston M. & S. J.* **167**:918, 1912.
- McFadden, G. D. F.: Mesenteric Lymphadenitis and Its Clinical Manifestations, *Brit. M. J.* **2**:1174, 1927.
- MacFadyen, A., and MacConkey, A.: An Experimental Examination of Mesenteric Glands, Tonsils and Adenoids, *Brit. M. J.* **2**:129, 1903.
- MacKee, G. M.: X-Rays and Radium in the Treatment of Diseases of the Skin, Philadelphia, Lea & Febiger, 1927.
- Mächtle, H.: Ueber die primäre Tuberkulose der mesenterialen Lymphdrüsen, *Beitr. z. klin. Chir.* **59**:50, 1908.
- Magendie, F.: *J. de physiol. expér.* **5**:399, 1825; quoted by Garrison.
- Marshall, C. J.: Simple Ileo-Caecal Lymphadenitis, *Brit. M. J.* **1**:631, 1928.
- Mascagni, P.: Vasorum lymphaticorum corporis humani historia et iconographia, Senis, ex typog. P. Carli, 1787; quoted by Wullenweber and Garrison.
- Matyas, M.: Ueber die Bauchtuberkulose, mit besonderer Berücksichtigung der Mesenterialdrüsentuberkulose, *Zentralorg. f. d. ges. Chir.* **11**:84, 1921.
- Mettenleiter, M.: Ueber primäre Mesenterialdrüsentuberkulose bei Kindern, *Deutsche Ztschr. f. Chir.* **199**:120, 1926.
- Mischel, K.: Strangulationsileus durch Lymphadenitis mesaraica tuberkulosa, *Zentralbl. f. Chir.* **57**:865, 1930.
- Molyneux, E. S.: Radium as a Curative Agent for Tuberculous Glands, *Lancet* **2**:804, 1922.
- Monro, A.: (Secundus): De venis lymphaticis valvulosis et de earum in primis origine, Lipsiae, 1760; Berlin, G. A. Lang, 1761; quoted by Wullenweber.
- Morley, J.: Clinical Aspects of Abdominal Tuberculosis, *Brit. M. J.* **1**:383, 1922.
- Most, A.: Chirurgie der Lymphgefäße und der Lymphdrüsen, in von Bruns, P.: *Neue deutsche Chirurgie*, Stuttgart, Ferdinand Enke, 1917, vol. 24.
- Müller, J.: Erkrankungen des Verdauungskanal, des Bauchfells und der grossen Unterleibsdrüsen bei Tuberkulose, in Brauer, L.; Schröder, G., and Blumenfeld, F.: *Handbuch der Tuberkulose*, Leipzig, Johann Ambrosius Barth, 1923, vol. 3, p. 440.
- Murray, H. L.: A Case of Mesenteric Thrombosis in Youth Originating from a Caseating Tuberculous Gland, *Brit. J. Child. Dis.* **11**:304, 1914.
- Newbolt, G. P.: Tuberculous Mesenteric Glands and Some Abdominal Conditions They Give Rise To, *Brit. M. J.* **2**:1101, 1911.

- Opie, E. L.: First Infection with Tuberculosis by Way of the Intestinal Tract, *Am. Rev. Tuberc.* **4**:641, 1920.
- Orth, O.: Kompression der Flexura duodenojejunalis durch Drüsen, *Zentralbl. f. Chir.* **55**:2508, 1928.
- Osler, W., and McCrae, T.: *The Principles and Practice of Medicine*, ed. 10, New York, D. Appleton & Company, 1926.
- Parker, D. W.: Tuberculous Mesenteric Glands Simulating Appendicitis, *Boston M. & S. J.* **167**:918, 1912.
- Pecquet, J.: *Experimenta nova anatomica*, Paris, J. Tollium, 1651, quoted by Garrison.
- Philip, R.: Tuberculosis of the Lymphatic System, *Brit. M. J.* **1**:129, 1922.
- Pribram, B. O.: Die Lymphangitis mesenterialis als abdominelle Herdinfektion. Substrat der peritonealen Adhäsionen und Bindeglied zwischen den sogenannten zweiten Krankheiten, *Arch. f. klin. Chir.* **160**:362, 1930.
- Rawitzkaja, A. J.: Ein Fall von letaler Blutung als Folge einer Tuberkulose der Mesenterialdrüsen, *Beitr. z. Klin. d. Tuberk.* **71**:790, 1929.
- Richardson, M. H.: Acute Tuberculosis of the Mesenteric Lymph Glands, *New York State J. Med.* **1**:143, 1901.
- Rilliet, F., and Barthelz, E.: *Maladies des enfants*, ed. 3, Paris, F. Alcan, 1861, vol. 3, p. 846.
- Riseley, E. H.: The Preoperative Diagnosis of Tubercular Mesenteric and Retro-peritoneal Glands, *Boston M. & S. J.* **172**:253, 1915.
- Rudbeck, O.: Nova exercitatio anatomica exhibens ductos hepaticos aquosos et vasa glandularum serosa, *Westerds*, 1653; quoted by Garrison.
- Ruescher, E.: Ein Fall von Mesenterialdrüsentuberkulose kompliziert durch Arrosion eines Mesenterialgefäßes, *Ztschr. f. Tuberk.* **47**:383, 1927.
- Sata, A.: Meine Tuberkuloseforschungen aus den letzten Jahren (1918-1926), *Ztschr. f. Tuberk.* **48**:6, 1927.
- Scammon, R. E.; Harris, J. A.; Jackson, C. M., and Paterson, D. G.: *The Measurement of Man*, Minneapolis, University of Minnesota Press, 1930, p. 193.
- Schalij, J.: Calcification of Mesenteric Glands with Intestinal Spasm, *Nederl. tijdschr. v. geneesk.* **1**:734 (Feb. 11) 1928.
- Schmieden: Diagnose und operative Behandlung der Mesenterialdrüsentuberkulose, *Med. Klin.* **16**:219, 1920.
- Sennels, A.: Hyperplasia glandularum mesenterii, adenitis meseraica, *Ugesk. f. læger* **87**:1125, 1925.
- Shiota: Zur Pathologie und Therapie der tumorbildenden stenosierenden Ileocaecaltuberkulose, *Arch. f. klin. Chir.* **87**:982, 1908.
- Short, A. R.: Symptoms Due to Mesenteric Lymphadenitis, *Lancet* **2**:909, 1928.
- Sprengel: Wurmfortsatzentzündung, *Deutsche Gesellsch. f. Chir.* **34**:47, 1906.
- Sternberg, A.: Zur Diagnostik der Mesenterialdrüsentuberkulose, *Ztschr. f. Tuberk.* **47**:117, 1927.
- Still, G. F.: *Common Disorders and Diseases of Childhood*, ed. 3, New York, Oxford University Press, 1915, p. 424.
- Strömbeck, J. P.: Mesenteric Lymph-Adenitis: A Clinical Study, *Acta chir. Scandinav. (supp. 20)* **70**:1, 1932.
- Struthers, J. W.: Mesenteric Lymphadenitis Simulating Appendicitis, *Edinburgh M. J.* **27**:22, 1921.
- Thiemann, H.: Chirurgische Tuberkulose der Mesenterial- und Bronchialdrüsen, *Arch. f. klin. Chir.* **91**:245, 1909.
- Ungar: Die Behandlung der intraperitonealen Tuberkulose; Laparotomic, *München med. Wchnschr.* **56**:778, 1909.

- Valentin, E.: Der Ureterverschluss durch Mesenterialdrüsentuberkulose, *Arch. f. klin. Chir.* **118**:189, 1921.
- Varney, H. R.: Results in Radiotherapy, *J. A. M. A.* **40**:1577 (June 6) 1903.
- Wagner, J.: Acute Mesenteric Lymphadenitis Following Trauma and Simulating Acute Appendicitis, *Internat. J. Med. & Surg.* **38**:113, 1925.
- Wakely, C. P. G.: A Case of Calcified Gland of Unusual Size Giving Rise to Dysphagia, *Brit. J. Surg.* **10**:295, 1922.
- Walker, J. T.: Relation of Calcified Abdominal Glands to Urinary Surgery, *Lancet* **2**:1213, 1922.
- Walsham, H.: The Channels of Infection in Tuberculosis Together with the Conditions, Original or Acquired, Which Render the Different Tissues Vulnerable, *Lancet* **2**:831, 1905.
- Wantoch, H.: Ueber tiefsitzende Duodenalstenose infolge atuberkulöser oder tuberkulöser Lymphdrüsenanschwellungen der Mesenterialwurzel, *Deutsche Ztschr. f. Chir.* **226**:135, 1930.
- Weil, E. A.: Roentgenotherapy of Peripheral Tuberculous Adenopathy, *Am. J. Roentgenol.* **4**:449, 1917.
- Werner, P. C. F., and Feller, C. G.: *Vasorum lacteorum atque lymphaticorum anatomico-physiologica descriptio*, Leipzig, S. L. Crusium, 1784, quoted by Wullenweber.
- Whitworth, A. W. T.: Note on a Case of Tuberculosis of the Mesenteric Glands, with Ulceration into the Superior Mesenteric Artery, *Lancet* **2**:157, 1908.
- Wilensky, A. O.: Mesenteric Lymphadenitis, *M. J. & Rec.* **98**:770, 1920.
- and Hahn, L. J.: Mesenteric Lymphadenitis, *Ann. Surg.* **83**:812, 1926.
- Williams, F. H.: *The Roentgen-Rays in Medicine and Surgery*, New York, The Macmillan Company, 1903.
- Wilms: Ueber die Sensibilität und Schmerzempfindung der Bauchorgane, *Deutsche Ztschr. f. Chir.* **100**:372, 1909.
- Woodhead, G. S.: *Tuberculosis Mesenterica and Pulmonary Tuberculosis*, Rep. Lab. Roy. Coll. Phys. **1**:179, 1889.
- Wullenweber, E.: *Zur normalen und pathologischen Anatomie der Mesenterialdrüsen*, Kiel, A. F. Jensen, 1889.
- Young, M., and Turnbull, H.: An Analysis of the Data Collected by the Status Lymphaticus Investigation Committee, *J. Path. & Bact.* **34**:213, 1931.

# CLINICAL USE OF A PLASTIC PYLOROJEJUNOSTOMY IN CHRONIC DUODENAL ULCER

GOLDER L. McWHORTER, M.D., Ph.D.  
Assistant Clinical Professor in Surgery, Rush Medical College  
of the University of Chicago  
CHICAGO

The satisfactory results of surgical treatment of such a variable pathologic lesion as chronic peptic ulcer should be increased by the selection of the safest and most satisfactory operation for each condition.

The introduction of a plastic pylorojejunostomy with excision of the ulcer, when it is indicated, offers considerably less risk than a gastric resection. It will also permit side-tracking the ulcer with a more normal gastric physiology and less danger of jejunal ulcer than by closing the pylorus and performing a gastrojejunostomy.

A number of factors have a bearing on the choice of surgical treatment of peptic ulcer.

In the etiology of ulcer, infection has been considered of both primary and secondary importance. While acute ulcers may be produced experimentally by infection, it is likely that similar lesions arising clinically promptly heal in the absence of a spasmophilic tendency or ulcer diathesis (Alvarez<sup>1</sup>).

Ivy and Fauley<sup>2</sup> failed to produce chronic ulcer by direct infection of the gastric antrum. They explained the genesis of ulcer in man by emotional disturbances which, through pylorospasm, disturb the emptying of the stomach and may mechanically rupture a blood vessel in the mucosa. Gastric retention causes augmented motility and prolongs the contact of a highly acid gastric juice which has been shown to lower the resistance of the mucosa. The corrosive action of the acid gastric juice has been demonstrated by Mann and his associates<sup>3</sup> to be the most potent factor in the genesis of chronic ulcer by its almost constant occurrence after gastrojejunostomy when the duodenal contents are diverted to the ileum.

---

Read before the Western Surgical Association, Cincinnati, Dec. 8, 1933.

1. Alvarez, W. C.: The Causes of Peptic Ulcer, *Am. J. Surg.* **18**:207, 1932.

2. Ivy, A. C., and Fauley, G. B.: The Factors Concerned in Determining the Chronicity of Ulcers in the Stomach and Upper Intestine, *Am. J. Surg.* **11**:531, 1931.

3. Mann, F. C., and Williamson, C. S.: The Experimental Production of Peptic Ulcer, *Ann. Surg.* **77**:409, 1923. de Takáts, G., and Mann, F. C.: *Ann. Surg.* **85**:698, 1927.

Ivy and Fauley demonstrated that a number of additional factors are also present. They sutured the end of the stomach to the end of the jejunum, with diversion of duodenal juices to the ileum, and ulcers occurred in all experiments, but after suturing to the side of the jejunum, ulcers occurred in only 45 per cent. When the duodenal juices were drained into the antrum after an end-to-end gastrojejunostomy, ulcers occurred in only 16 per cent of experiments, but when later diverted to the ileum, ulcers appeared in 87 per cent. After suture of the end of the stomach to the side of the duodenum, with diversion of alkaline juices, ulcer occurred in only 10 per cent of the subjects of the experiment. After section of the duodenum 1 inch (2.5 cm.) below the pylorus and suture to the jejunum, with diversion of the duodenal contents, ulcers developed below the suture line in 66 per cent of the subjects. The method of anastomosis would seem to be more important than the susceptibility of the mucosa to ulcer.

The results of the experiments suggest that a jejunal ulcer would be less than one half so likely to occur after a properly performed end-to-side pylorojejunostomy as after a gastrojejunostomy.

Longitudinal anastomosis of the jejunum to the pylorus with the proximal loop attached to the incision in the antrum might result in better regurgitation than anastomosis at right angles. If the duodenal secretions prove to be diverted into the stomach as well after a pylorojejunostomy as after section of the jejunum and reimplantation into the antrum (a somewhat more complicated technic) the incidence of jejunal ulcer should be reduced to about one-tenth that after a gastrojejunostomy.

The short loop of jejunum may be sutured in position above the transverse mesocolon after anastomosis to the pylorus, if desirable. It is possible that a slight jejunal stasis below the stoma may aid in the prevention of a recurrent ulcer, although I have seen duodenal stasis associated with duodenal ulcer.

Contributing factors to ulcer have been proved to be: a small stoma or stenosis of the pylorus; roughage in the diet which delays emptying and traumatizes tissue; the motor drive; trauma at operation; failure of normal neutralization by duodenal juices, and a gradual increase of susceptibility of the mucosa to the acid juices from above downward in the intestine.

Pyloric stenosis alone has been shown experimentally not to give rise to gastric ulcer, but may delay its healing. Isolated pouches of the whole stomach have resulted in peptic ulcers near the fistula, but none along the lesser curvature (Moutier<sup>4</sup>).

---

4. Quoted by Alvarez.<sup>1</sup>

Morton<sup>5</sup> showed the presence of a mechanical factor by reducing the force of ejection of acid chyme from the stomach, with fewer ulcers.

Keppich<sup>4</sup> permitted the duodenal secretions to flow high up into the fundus in a few experiments with a low end-to-side gastrojejunostomy, and found fewer jejunal ulcers after removing the distal end of the stomach. Koennecke<sup>4</sup> isolated the pars pylorica with the first part of the duodenum and anastomosed them to the ileum and found no ulcers, refuting the aforementioned implication that the secretions of the antrum and duodenum might predispose to ulcer.

Other factors than the acid gastric juice must predispose to ulcer, since under normal conditions acute lesions of the stomach heal readily. In addition, various organs and parts of the intestine have been transplanted into the stomach wall without being digested, as long as the circulation was intact (Ivy and Fauley). Although transplants of jejunal mucosa into the anterior wall of the stomach and antrum have not resulted in ulcers (Ivy and Fauley), Mann obtained them on transplantation into the lesser curvature.

Goldberg<sup>6</sup> and Harper<sup>7</sup> found that a peptic ulcer always developed in the small intestine where it was sutured to a Pavlov or acid-secreting pouch of the stomach.

However, Harper showed that when a secreting pouch of the antrum was anastomosed to the intestine free acid was not present and no ulcer formed. He was able to prevent ulcers adjacent to Pavlov pouches by coating the mucosa with an emulsion of gelatin, acacia, olive oil and lecithin twice a day.

Alvarez stated that certain foods, including the peptones, exerted a protective action on the cells of the mucosa during digestion.

The importance of peristalsis was shown by Bollman and Mann,<sup>8</sup> who found no leak from a gastric fistula into the intestine and no ulcer if peristalsis was directed toward the stomach.

Pathologically, a chronic peptic ulcer shows sclerosis of the blood vessels, which increases with the chronicity of the condition (Wellbrock<sup>9</sup>). The vascular fibrosis, with the indurated connective tissue bed, must be important factors in the failure to heal under favorable

---

5. Morton, C. B.: Observations on Peptic Ulcer: A Method of Producing Chronic Gastric Ulcer, *Ann. Surg.* **85**:207, 1927.

6. Goldberg, S. S.: A Method of Producing Peptic Ulcer Experimentally. *Ann. Surg.* **96**:155, 1932.

7. Harper, F. R.: Experimental Peptic Ulcer, *Proc. Staff Meet., Mayo Clin.* **7**:318 (June 1) 1932.

8. Bollman, J. L., and Mann, F. C.: Peptic Ulcer in Experimental Obstructive Jaundice, *Arch. Surg.* **24**:126 (Jan.) 1932.

9. Wellbrock, W. L. A.: Duodenitis and Duodenal Ulcer, *Ann. Surg.* **91**:533 (April) 1930.

medical or surgical treatment. The frequent occurrence of large arteries in the base of the ulcer explains the severe hemorrhages.

In the healing of chronic peptic ulcer there are four fundamental objectives: first, rest to the ulcer; second, improvement of the local blood supply; third, removal of the cause, and, fourth, restoration of normal gastric function.

Various medical treatments, including attempts to neutralize the acid secretions, have resulted in a large percentage of failures.

Brown<sup>10</sup> reported from a follow-up of one thousand, two hundred and twenty-four patients that 49 per cent were cured and 16.5 per cent improved by the Sippy treatment, which included rest under hospital management. He believed that the poor results in about 20 per cent of the patients were due to extensive fibrosis of the ulcer from lack of early medical treatment, and that this group should have received surgical treatment.

Alvarez stated that no medical treatment neutralizes the acid secreted during the night.

Pylorospasm has been considered as one of the important factors to control in the treatment of ulcer, since it produces retention with high acidity and may prevent normal regurgitation of the duodenal contents.

Alvarez reported that experimentally the neutralizing power of the duodenal secretions is greater than that of the pancreatic secretions and the latter is better than that of bile.

The stomach may be divided into two main portions by the incisura angularis: the fundus, and the antrum, or pyloric part. Experimental work has shown that the fundus is less actively motile and acts as a reservoir, while the muscular antrum is chiefly concerned with mixing and expelling the food. The mechanism controlling the pyloric sphincter is obscure, but it responds to the acidity of the stomach and duodenal contents as well as to the type and consistency of food (Howell<sup>11</sup>).

Bayliss<sup>12</sup> has shown that normally the amount of regurgitation of duodenal juices increases with the acidity of the gastric contents.

The secretion of the antrum is always alkaline (Howell). The mucosa contains no acid-secreting cell, but only a mucoid type of cell (Bensley<sup>13</sup>).

Edkins<sup>14</sup> stated that products of digestion in contact with the antrum stimulate gastric secretion by an action of the hormones. However,

10. Brown, Ralph C.: Results of Medical Treatment of Peptic Ulcer, J. A. M. A. 95:1144 (Oct. 18) 1930.

11. Howell, W. H.: Textbook of Physiology, ed. 10, Philadelphia, W. B. Saunders Company, 1927.

12. Bayliss, W. M.: Principles of General Physiology, New York, Longmans, Green & Co., 1924.

13. Bensley, quoted by Howell.<sup>11</sup>

14. Edkins, quoted by Bayliss.<sup>12</sup>



it has been shown by Priestley and Mann<sup>15</sup> that there is no change in the gastric acidity in Pavlov pouches after either exclusion or excision of the pyloric part of the stomach.

In the surgical treatment of peptic ulcer Balfour<sup>16</sup> stated that all requirements for a good result are satisfied by removal of the lesion and by establishment of an adequate means of emptying the stomach.

Bevan<sup>17</sup> observed that, in general, the best surgical treatment for duodenal ulcer was a gastrojejunostomy and for gastric ulcer, a resection of the stomach.

In small ulcers, Balfour advocated either a pyloroplasty or a gastrojejunostomy, with local excision when possible. In lesions of the posterior wall of the duodenum he advised excision of the ulcer with a cautery or a knife, followed by a pyloroplasty. Judd and Hazeltine<sup>18</sup> stated that such operations can be done in 50 per cent of patients with duodenal ulcer with slightly better results and with a lower mortality than a gastro-enterostomy.

Gastroduodenostomy and pyloroplasty with or without excision of the ulcer have not been used widely because of the frequency of adhesions, the large number of ulcers of the posterior wall and the necessity for a more exacting technic. There is also a rather frequent recurrence of the ulcer and a persistence of symptoms (Bevan; Meyer and Rosi;<sup>19</sup> Horsley;<sup>20</sup> Hurst<sup>20</sup>). Pyloroplasty in ulcers of the posterior wall would not seem indicated, since either the ulcer is left or excision of it leaves a new wound which may leak or fail to heal.

Walton<sup>21</sup> stated that neutralization of the acid secretions did not take place at a high enough level after gastroduodenostomy to be satisfactory in ulcers of the lesser curvature.

---

15. Priestley, J. T., and Mann, F. C.: Gastric Acidity with Special Reference to the Pars Pylorica and Pyloric Mucosa: Experimental Study, *Arch. Surg.* **25**:395 (Aug.) 1932.

16. Balfour, D. C.: (a) Management of Lesions of the Posterior Wall of the Duodenum, *Surg., Gynec. & Obst.* **49**:806 (Dec.) 1929; (b) Gastric Ulcer and Its Treatment, in *Collected Papers of Mayo Clinic*, Philadelphia, W. B. Saunders Company, 1931, vol. 23, p. 70; (c) The Advisability of Early Operation for Duodenal Ulcer, *West. J. Surg.* **40**:28, 1932; (d) Results of Gastro-Enterostomy for Ulcer of the Duodenum and Stomach, *Ann. Surg.* **92**:558, 1930; (e) Causes of Unsatisfactory Results in the Surgical Treatment of Peptic Ulcer, *Collected Papers of Mayo Clinic*, Philadelphia, W. B. Saunders Company, 1930, vol. 22, p. 56.

17. Bevan, Arthur D.: *S. Clin. North America* **12**:18 (Feb.) 1932.

18. Judd, E. S., and Hazeltine, M. E.: The Results of Operation for Excision of Ulcer of the Duodenum, *Ann. Surg.* **92**:563 (Oct.) 1930.

19. Meyer, K. A., and Rosi, P. A.: Successive Perforation of Two Anastomotic Marginal Ulcers in the Same Patient, *S. Clin. North America* **13**:1251 (Oct.) 1933.

20. Quoted by Meyer and Rosi.<sup>19</sup>

21. Walton, A. J., in *Nelson Loose-Leaf Living Surgery*, New York, T. Nelson & Sons, 1928, vol. 5, chap. 2, p. 43.

Fortunately, the percentage of cures after a gastrojejunostomy when the ulcer has been left to heal, has been very high. Balfour<sup>17b</sup> reported 89 per cent of satisfactory results in gastric ulcers and Gatewood,<sup>22</sup> 82 per cent, including all peptic ulcers. Gaither,<sup>23</sup> in a personal follow-up, found 80 per cent of complete cures after gastrojejunostomy, and 72 per cent of cures after various conservative operations, with 19 per cent improved and only 9 per cent unimproved. He stated that in view of the low mortality as compared to subtotal resection, there was no justification for displacing the conservative types of operation. Alvarez stated that in duodenal ulcer gastrojejunostomy is the best operation, as from 80 to 90 per cent of the patients are relieved.

Jejunal ulcer occurs with varying frequency, but its incidence is probably about 3 per cent after gastrojejunostomy (Bevan; Balfour; Alvarez; Benedict<sup>24</sup>). However, it may be very high when there is a stenosis or exclusion of the pylorus. Schwarz<sup>4</sup> reported stenosis in eighty-three of one hundred and thirty cases of gastrojejunal ulcer. Eiselsberg<sup>4</sup> found ulcers of the jejunum in over 25 per cent of cases in which exclusion of the pylorus had been done with a gastrojejunostomy.

Exclusion above the antrum is sometimes done (Devine;<sup>25</sup> Alvarez). The contention is that by leaving the antrum, duodenal peristalsis is strengthened, and better neutralization is obtained at the gastrojejunostomy stoma. However, there may be a weaker stimulation of the alkaline secretions by food emptying only into the jejunum and actually less efficient duodenal expulsion of the juices, since jejunal ulcers still occur and even the duodenal ulcer does not always heal.

Jejunal ulcer is more likely to follow any method of gastrojejunostomy which prevents easy access of duodenal secretions about the stoma (Mann) and also inadequate neutralization or mixing in the stomach.

The gastrojejunostomy stoma, Walton believed, should be at the greater curvature. If made higher, it will not empty readily unless the patient is lying down. He believed that if the stoma is placed near the pylorus, especially if the ulcer is near it, the antrum will greatly assist evacuation.

22. Gatewood: Immediate Mortality and Late Results of Operations for Peptic Ulcer Performed in Presbyterian Hospital, Chicago, Between 1915 and 1930, *Ann. Surg.* **92**:554 (Oct.) 1930.

23. Gaither, E. H.: Eventual Results of Gastric Surgery, *J. A. M. A.* **101**:966 (Sept. 23) 1933.

24. Benedict, E. B.: Jejunal Ulcer, *Surg., Gynec. & Obst.* **56**:807 (April) 1933.

25. Devine, H. B.: Basic Principles and Supreme Difficulties in Gastric Surgery, *Surg., Gynec. & Obst.* **40**:1 (Jan.) 1925.

Experimentally, Cannon and Murphy<sup>26</sup> found food passing entirely through the pylorus after gastrojejunostomy, but clinically the stomach empties through both the pylorus and the stoma. The amount passing either is probably dependent on their relative size, the amount of spasm (Walton) and the location of the stoma.

The healing of a duodenal ulcer after a gastrojejunostomy may be dependent on the improved contact with alkaline juices, together with lessened acidity in the stomach and more rapid emptying. The frequency of return of a healed duodenal ulcer following the taking down of a gastrojejunostomy for jejunal ulcer is well known.

Lahey<sup>27</sup> reported the reactivation of a duodenal ulcer after a subtotal resection of the stomach with the ulcer excluded, before removal at a second-stage operation. He stated that any satisfactory surgical treatment must offset the effects of pylorospasm either by a direct operation on the sphincter or by a gastro-enterostomy.

Following gastrojejunostomy, undetermined factors sometimes delay evacuation and prolong the secretion of acid. I<sup>28</sup> have observed this experimentally in animals with a Pavlov pouch and also clinically.

The incidence of gastrojejunal ulcer following gastric resection is believed by Strauss and his co-workers<sup>29</sup> to be between 1 and 2 per cent. St. John<sup>30</sup> reported it after 3.6 per cent of gastric resections and Gatewood after 10 per cent.

Lahey stated that the mortality of primary gastric resection is too high, even if as low as 6.7 per cent. He found the mortality was 20 per cent after resections for jejunal ulcer. Postoperative jejunal paralysis or local peritonitis may cause acute gastroduodenal dilatation after jejunal resections. If unrelieved by a duodenal tube, reoperation with short-circuiting or jejunostomy may save the patient's life.

In large ulcers Balfour advised a partial duodenectomy with gastric resection, if too much does not have to be removed. He reported resection in 75 per cent of chronic gastric ulcers in 1931. Emerson and Czirer<sup>31</sup> reported resection of all callous ulcers of the stomach.

---

26. Cannon, W. B., and Murphy, F. T.: *Movements of the Stomach and Intestines in Some Surgical Conditions*, *Ann. Surg.* **43**:512, 1906.

27. Lahey, F. H.: *The Selection of the Operative Procedure for Various Gastric and Duodenal Lesions*, *S. Clin. North America* **13**:541 (June) 1933.

28. McWhorter, G. L.: *Some Clinical and Experimental Observations on Gastric Acidity*, *Am. J. M. Sc.* **155**:672, 1918.

29. Strauss, A. A.; Bloch, L., and Friedman, J. G.: *Gastrojejunal Ulcer*, *J. A. M. A.* **90**:181 (Jan. 21) 1928. Strauss, A. A.; Bloch, L.; Friedman, J. G.; Meyer, J., and Parker: *Subtotal Gastrectomy for Duodenal Ulcer*, *ibid.* **95**:1883 (Oct. 18) 1930. Strauss, A. A., in discussion on Gaither, E. H.: *Gastric Surgery*, *ibid.* **101**:966 (Sept. 23) 1933.

30. St. John, F. B.: *Ann. Surg.* **92**:597, 1930.

31. Emerson, E. C., and Czirer, L.: *Surg., Gynec. & Obst.* **56**:927 (May) 1933.

The surgical treatment for peptic ulcer by resection of the anterior half of the pyloric sphincter was reported by Deaver and Burden<sup>32</sup> in a series of cases to give as good results as either gastrojejunostomy or resection of the stomach.

A wedge resection of the fundus of the stomach has been advocated by Connell<sup>33</sup> for chronic ulcer. This operation removes a large part of the acid-secreting mucosa, but does not interfere with the pyloric mechanism.

Roholm<sup>34</sup> abandoned circular resections of the stomach because of frequent recurrent ulcers in the scar.

The choice of any one of a number of conservative operations demands further knowledge of the disturbed physiologic relations and the benefits to be expected by different operations on the type of ulcer present.

Recognition of the extent of pathologic changes is necessary to determine the importance of excision of the ulcer and the most conservative operation which should give relief.

The persistence of old ulcers due to fibrosis after good medical management or a conservative operation probably explains the lack of relief in many patients. Since many callous ulcers are on the posterior wall of the duodenum, either excision or exclusion by a conservative operation may be obtained by a pylorojejunostomy.

The method of plastic pylorojejunostomy described here permits excision of the ulcer without resection of the stomach. If excision of the ulcer is not advisable, the duodenum may be closed above the ulcer, which can be resected later if desirable.

There are both technical and physiologic advantages of pylorojejunostomy over the Billroth I and II technics or their modifications (Bevan), a gastrojejunostomy, a partial gastric exclusion, or a gastric resection. The motor mechanism of the stomach and antrum is maintained for normal mixing and emptying. The alkaline juices of the antrum are retained. The dangerous ulcers of the lesser curvature after resection are avoided. Mechanical drainage of the stomach may be improved by swinging the antrum down and to the left through the transverse mesocolon.

Theoretical objections are supported by inconclusive physiologic experiments. Resection of the antrum, which has been thought to lessen the stimulating action of the hormones and relieve the muscular

32. Deaver, J. B., and Burden, V. G.: *Ann. Surg.* **92**:533 (Oct.) 1930.

33. Connell, F. G.: Resection of the Fundus of the Stomach for Peptic Ulcer, *Ann. Surg.* **96**:209, 1932.

34. Roholm, K.: Value of Circular Resection in Chronic Gastric or Duodenal Ulcer, *Ugesk. f. læger* **95**:573 (May 18) 1933; abstr., *J. A. M. A.* **101**:332 (July 22) 1933.

motor drive, has given no better results than a gastrojejunostomy (Roholm). Crohn<sup>35</sup> reported that there was achylia in all cases he had followed up in which subtotal gastrectomy had been done. Neither small nor wide resections of the stomach have fulfilled expectations in the treatment of ulcer. A recurrent ulcer occurs frequently, even after the Billroth I operation (Bevan).

Unless achylia is obtained by radical resection the preservation of the antrum should aid neutralization. Pylorojejunostomy permits this with conservation of normal physiologic relations, although it seems evident that the pyloric sphincter should be cut well into the antrum, permitting a wide anastomosis to the jejunum.

Jejunal ulcers would seem to be more frequent when the anastomosis is made to the acid-bearing part of the stomach than to the antrum, although there are several factors involved, such as the size and location of the stoma, the emptying time, the motor drive and the intragastric and extragastric mixing of the alkaline and acid juices.

Andrews<sup>36</sup> has recently supported the growing evidence that there is a tendency to the formation of a jejunal ulcer by the pouring out of unneutralized acid juice when the stoma is placed high up in the acid-secreting part of the stomach.

The small number of serious complications following conservative surgical procedures in patients not completely relieved with good medical management is assurance that if the proper operation is performed fewer failures will result.

A competent medical authority (Brown<sup>19</sup>) has stated that patients with callous ulcers should be treated surgically. Conservative operations will relieve the majority. When excision of the ulcer seems indicated and a pyloroplasty is impossible or the lesion is on the posterior wall of the duodenum, a pylorojejunostomy is far safer than gastric resection. It may also be used in a patient whose condition is otherwise inoperable or who is a bad risk. The chances of a jejunal ulcer may be minimized by proper technic and medical management. Reoperation should be easier than after gastric resection.

The radical gastric resection should be reserved for patients with extensive lesions shown to be resistant to conservative operations. Until knowledge or adequate tests have been acquired to determine which complications occurring after conservative operations will not occur after radical ones, one should choose the former. Conservative surgical intervention for types of ulcer shown to resist medical treatment is consistent with the routine medical treatment for all uncomplicated cases of early peptic ulcer.

---

35. Crohn, B. B., in discussion on Eggleston, E. L.: *Pathologic Conditions Secondary to Achlorhydria*, J. A. M. A. **97**:1216 (Oct. 24) 1931.

36. Andrews, E.: *Jejunal Ulcer*, S. Clin. North America **13**:1251 (Oct.) 1933.

## REPORT OF A CASE

*Diagnosis.*—The following case was one of chronic perforating duodenal ulcer into the pancreas.

*History.*—J. W., a German man, aged 53, was examined on Feb. 19, 1933. The present complaint was "stomach trouble" for fifteen years, consisting of severe epigastric distress and frequent vomiting. He was rarely free from pain for more than two or three weeks at a time, but it was worse in the fall and winter.

The distress and pain usually came on within three or four hours after eating. This had become worse during the preceding few months, and during the month prior to examination the pain had been almost constant. Certain foods, such as fat meat, cabbage, sauerkraut, condiments, salt, pepper, tomatoes, apples, bananas and tea, gave more distress. Until the previous month he had been able to take a light diet of milk, farina or oatmeal, eggs, celery, spinach, well cooked vegetables, cake and pie, except apple pie. During the previous month he ate practically nothing, and was afraid to take even milk. He had some relief by drinking hot water and vomiting during the preceding two years. Soda gave relief for a few minutes.

When he was working as a laborer, up to a few years previously, he ate rapidly.

Examination at a clinic five years before, revealed heart trouble and roentgen evidence of an ulcer of the duodenum. He had been treated for the cardiac condition ever since. For several years he had some dyspnea on exertion. He worked only seven months during the preceding five years and none during the last two and one-half years, owing to the cardiac and gastric complaints.

Chronic bronchitis had been present for about twenty-five years, with a rather dry cough.

He smoked about forty cigarets a day for fifteen years, often waking and smoking during the night. He never drank alcohol. He had had no previous illness except a few bad colds. He lost his teeth in an accident twenty years before and had used plates ever since.

His average weight was about 158 pounds (71.7 Kg.) up to five years before examination. He lost gradually from that time until at examination he weighed 110 pounds (49.9 Kg.). Some days during the previous year he lost 3 or 4 pounds (1.3 to 1.4 Kg.), and then regained it slowly.

Sugar was found in the urine about eight months before. He had been under treatment for this and for the ulcer since then.

Three months before examination he was treated for his ulcer for six weeks in a large hospital. He was in bed for four weeks on the Sippy diet. He was never free from pain except when his stomach was pumped. Heat and hot milk gave some relief from the severe pain. For the previous month, since leaving the hospital, although still on a diet and alkalis, the gastric symptoms had become worse, so that he was afraid to eat anything and had become very weak.

*Physical Examination.*—The patient was well developed, but considerably emaciated. False teeth were used. The lungs showed no definite changes.

An examination of the heart was made at the cardiac clinic on March 10. The pulse rate was 120 and the blood pressure 90 systolic and 80 diastolic. There was a presystolic and systolic murmur, indicative of aortic stenosis and regurgitation. An electrocardiogram showed a P R interval of 0.2 and a Q R S interval of 0.06. There was a slurring of the R wave in all three leads, with a notching in lead II. The T and P waves were normal in amplitude, but the voltage in all three leads was low. The consultant stated that myocardial damage had occurred, and that the patient was not a good operative risk.

There was considerable tenderness on abdominal palpation over the region of the duodenum, with some muscle spasm.

Roentgen examination showed a deformity of the first part of the duodenum characteristic of an ulcer perforating into the pancreas (fig. 1). There was increased gastric peristalsis. No six hour retention was present.

The urine before operation contained granular casts, occasional white blood cells and many bacteria, but no albumin or sugar.

Examination of the blood on April 12 showed: hemoglobin content, 81 per cent; red cells, 4,000,000; white cells, 7,000; polymorphonuclears, 60 per cent; small lymphocytes, 30 per cent, and large lymphocytes, 10 per cent. The Wassermann and Kahn tests were negative.

At this time the patient's heart had been thoroughly digitalized, and the cardiac rate was 60. There was no definite improvement in the gastric symptoms, and operation was decided on.

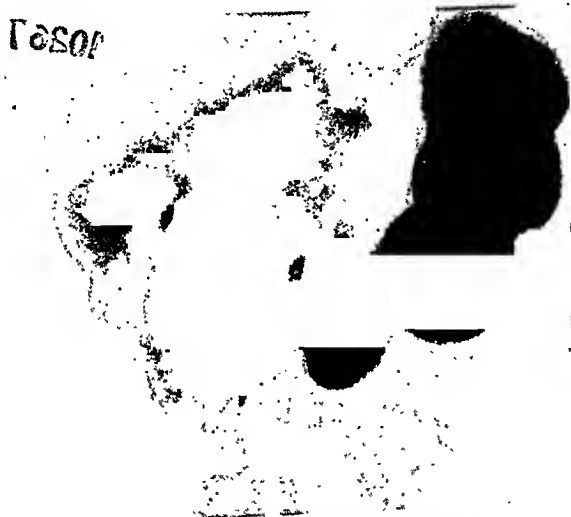


Fig. 1.—Roentgenogram taken before operation, showing a typical large perforating ulcer of the posterior wall of the duodenum.

*Operation.*—A plastic pylorojejunostomy was performed on April 19, with resection of a chronic perforating ulcer of the posterior wall of the duodenum into the pancreas. Regional local anesthesia with 0.5 per cent procaine hydrochloride was used.

A right paramedial incision was made. The stomach was normal, but the pylorus was considerably dilated. There was a large palpable mass involving the first part of the duodenum and the pancreas. There was some stippling on the lower side of the first part of the duodenum. The duodenum was incised just below the pylorus, and a huge ulcer crater was seen extending over the dilated posterior wall. The bed of the ulcer was formed by hard, dense, fibrous scar tissue on the pancreas, and measured 4.5 by 5 cm. in diameter. The active ulcer rim of the crater, which extended slightly forward on the anterior wall, was about 0.5 cm. wide and high.

The duodenum was cut across completely just below the pylorus and the ulcer rim excised, leaving as much of the anterior duodenal wall as possible. Only the active ulcer margin was removed (fig. 2), leaving the dense, boardlike fibrous base on the pancreas. There was little bleeding. The lower end of the duodenum

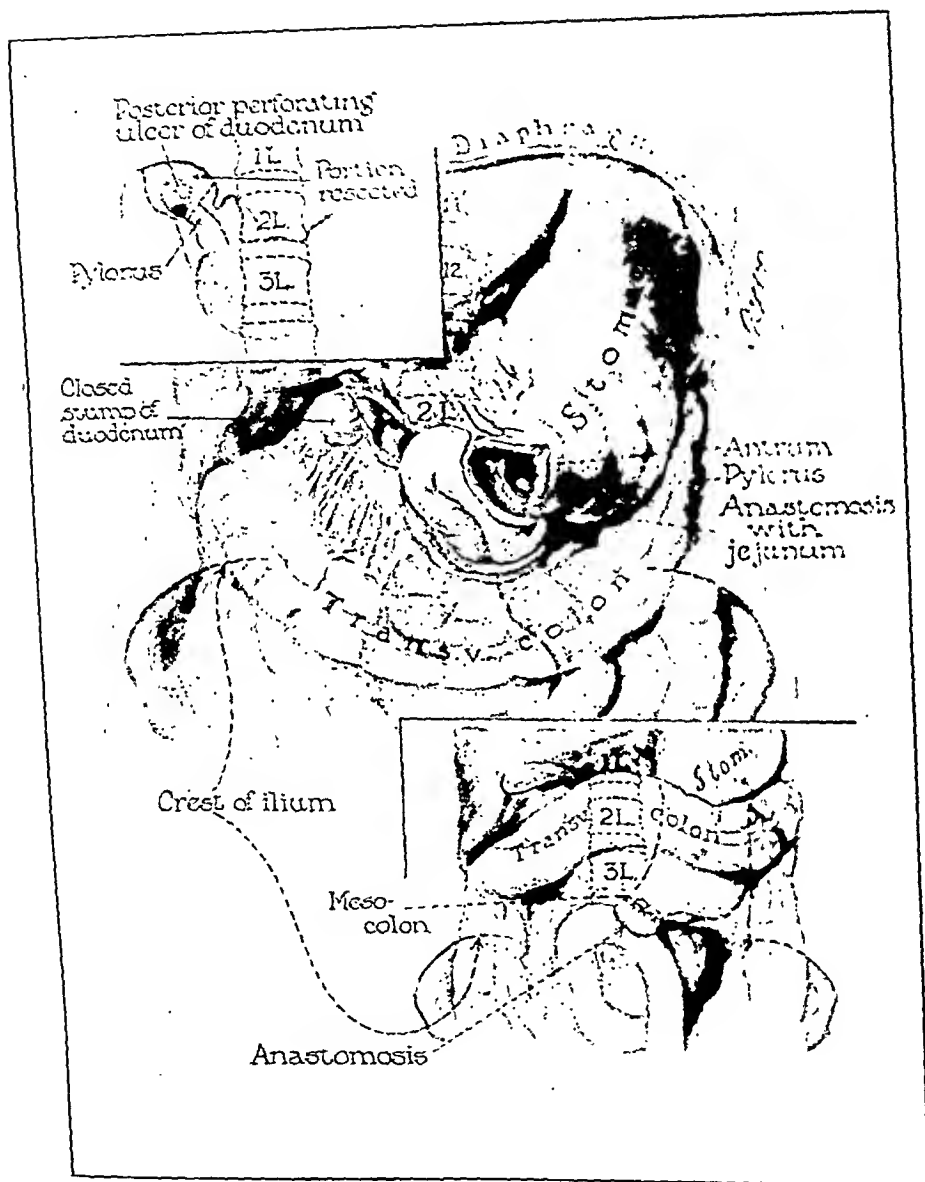


Fig. 2.—Technic of plastic pylorojejunostomy. The ulcer was excised and the stump of the duodenum invaginated. The lower end of the stomach was anastomosed to the jejunum and then fixed beneath the mesentery of the transverse colon. In the upper and lower insets the position of the stomach was copied from roentgenograms taken before and after operation.



was invaginated with fine silk sutures without using a clamp, following my technic reported elsewhere.<sup>37</sup>

The pyloric end of the stomach was freed for a short distance from the mesentery of the liver, the pancreas and the transverse colon, without injury to the blood supply. An opening was made in the transverse mesocolon similar to that for a gastrojejunostomy, and a loop of jejunum about 8 inches (20.3 cm.) from the ligament of Treitz was brought through it. A longitudinal cut was made through the anterior wall of the pylorus, extending about 1 inch (2.5 cm.) into the antrum of the stomach. A few blood vessels in the cut edges were ligated. The loop of jejunum was placed with the distal part downward against the enlarged pyloric end of the stomach and an anastomosis made, using three rows of chromic catgut sutures (fig. 3). The loop of jejunum with the attached pyloric end of the stomach was then pushed down through the hole in the mesentery. The edges were sutured to the antrum just above the line of anastomosis. A small collapsible drain was placed near the base of the ulcer on the pancreas, which was covered with omentum, and the abdomen closed.

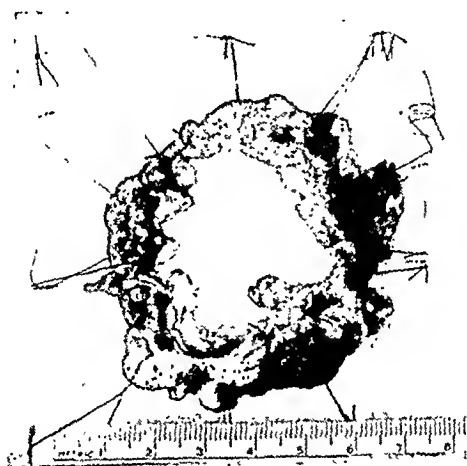


Fig. 3.—Excised perforating ulcer of the duodenum. The indurated fibrosed base was not removed.

Microscopic sections of the edge of the ulcer showed round cell infiltration, with only dense fibrous tissue at its base.

*Postoperative Course.*—There were no complications. The drain was removed on the second day.

The patient was given a bland diet, with no alkalis. Complete relief from the previous gastric distress was obtained.

Three months later there was a gain of 20 pounds with a general gain in strength. Eight months after operation there was a further gain of 23 pounds, to a weight of 153 pounds (69 Kg.).

Roentgenograms three and six months after operation showed the pyloric end of the stomach considerably lower and to the left of its former position (figs. 2, 4 and 5). There was excellent peristalsis with rapid emptying. One hour and fifteen minutes after a barium sulphate meal the stomach was almost empty. Four hours after the meal the barium was all in the ascending colon.

37. McWhorter, G. L.: An Original Method of Closure of a Partially Aperi-toneal or Short Intestinal End, *Surg., Gynec. & Obst.* 50:1037 (June) 1930.



Fig. 4.—Appearance six months after operation. The pyloric end of the stomach was lower and more to the left than before the operation.



Fig. 5.—The stomach was practically empty one and a fourth hours after a barium meal.

An Ewald meal was given, and showed a free hydrochloric acidity of 49 and a total acidity of 72. No blood was present.

Examination of the urine on Oct. 15, 1933, revealed considerable sugar, but otherwise gave negative results. A blood sugar test showed 272 mg. He was given a diabetic diet. His general condition was good. He was moderately active and able to do a little work, but his heart pounded on exertion. On examination twenty-two months after operation he was still on a diabetic diet and was working as a watchman. The urine was sugar-free and there were no complaints of gastric disturbance.

#### CONCLUSIONS

1. A conservative surgical procedure, when the general condition is satisfactory, is indicated in the treatment of many callous ulcers. Complications may require a radical operation and necessitate greater risk.
2. The surgical procedure should be adjusted to relieve the disturbed physiologic relations as well as the pathologic changes.
3. A plastic pylorojejunostomy has been used clinically with success when excision of an extensive callous duodenal ulcer perforating into the pancreas seemed imperative in a patient who was a poor risk.
4. Wider indications, including exclusion of a duodenal ulcer, may be found for pylorojejunostomy, which offers a better physiologic restoration than the most widely used operations and a lower mortality than gastric resection.

# STAPHYLOCOCCIC EMPYEMA AND PYOPNEUMOTHORAX

PATHOGENESIS, PATHOLOGY, SYMPTOMS AND TREATMENT

HAROLD NEUHOF, M.D.

AND

MAURICE BERCK, M.D.

NEW YORK

The occurrence and varying incidence of the staphylococcus in infections of the lung and of the pleura have been commented on by a number of observers, but the significance of pulmonopleural lesions due to the staphylococcus appears to have been overlooked. The literature consists essentially of statistical presentation of the incidence of the staphylococcus in pleuropulmonary infections, although staphylococcic pneumonia has been the subject of some separate discussion. Despite the fact that higher mortality has been noted, staphylococcic pleural infections have been included with the other bacteriologic varieties as if their pathogenesis, symptoms and treatment presented no appreciable differences. We believe that there are distinctive features in the pathogenesis and pathologic changes and in the treatment of staphylococcic pulmonopleural suppuration. The lesion in the form of empyema or pyopneumothorax will be described as an entity, and we shall attempt to show that its consideration as such leads to more clearly defined therapeutic measures.

## INCIDENCE

The available literature can be surveyed briefly, for it is chiefly concerned with incidence. As early as 1892 Netter<sup>1</sup> noted the staphylococcus in pure culture in 8 per cent of cases in a postmortem study of bronchopneumonia. Holt and Howland<sup>2</sup> in 1913, found the organism in 8 per cent of cases of empyema in children. In a study conducted at Mount Sinai Hospital in 1915 Wilensky<sup>3</sup> reported the incidence of staphylococcic empyema as 10 per cent. Chickering and Park<sup>4</sup> described

---

From the surgical service of Dr. Harold Neuhof and the laboratories of Mount Sinai Hospital.

1. Netter, P.: *Étude bactériologique de la bronchopneumonie*, Arch. de méd. expér. et d'anat. path. 4:28, 1892.

2. Holt, L. E., and Howland, J.: *The Diseases of Infancy and Childhood*, ed. 9, New York, D. Appleton & Company, 1926, p. 442.

3. Wilensky, A. O.: *Empyema of Thorax*, Surg., Gynec. & Obst. 2:501, 1915.

4. Chickering, H. T., and Park, J. H.: *Staphylococcus Aureus Pneumonia*, J. A. M. A. 72:617 (March 1) 1919.

a large number of cases of staphylococcic pneumonia occurring during an epidemic of influenza. The incidence of the staphylococcus as the cause of pneumonia is much lower under ordinary circumstances, as pointed out by Cole.<sup>5</sup> Nevertheless the staphylococcus is a common cause of empyema, the incidence given being as high as 22 per cent in one report (Heuer<sup>6</sup>).

The frequency and significance of staphylococcic empyema in infants will be referred to shortly. In a study of empyema in children below the age of 2 years, Rienhoff and Davison<sup>7</sup> found the staphylococcus in 19.5 per cent. Hart<sup>8</sup> reported an incidence of 17.5 per cent in a series of cases of empyema in children. Various authors have noted the incidence of staphylococcus in postmortem studies of bronchopneumonia in children: Lyon<sup>9</sup> reported 9.6 per cent, and Menter, Bailey and DeBone<sup>10</sup> reported 8 per cent. Reports of these and other investigators show that the staphylococcus is not a rare cause of pneumonia in children and is a common cause of empyema. If distinguishing features of pleural infections due to the staphylococcus have been noted they have not been described in any of the papers we have seen.

Because we observed the extraordinary frequency of staphylococcic empyema in very young infants in our service at Mount Sinai Hospital we examined the bacteriologic reports on all the cases of empyema from 1928 to 1932. There were 373 patients, of whom about half were children (182) and half adults (191). The incidence of the staphylococcus in adults was 5.7 per cent (11 cases) and in children under 13 years of age 17 per cent (31 cases). Much more striking, however, was the fact that 15 of the 21 cases of empyema in infants under 1 year of age were due to the staphylococcus (71 per cent). An additional significant fact is that half of all the cases of staphylococcic empyema in children in our series occurred in the first year of life.

#### PATHOGENESIS

Although this article deals with staphylococcic pleural infection, the causative pulmonary lesion obviously requires first consideration.

5. Cole, R. I.: *Acute Pulmonary Infections*, De Lamar Lectures, 1927-1928, Baltimore, Johns Hopkins University, School of Hygiene and Public Health, 1929.

6. Heuer, G.: *Acute Empyema*, *J. Thoracic Surg.* 1:461 (June) 1932; in *Nelson Loose-Leaf Living Surgery*, New York, T. Nelson & Sons, 1927, vol. 4, p. 503.

7. Rienhoff, W. F., and Davison, W. C.: *Empyema in Infants Under Two Years of Age*, *Arch. Surg.* 17:676 (Oct.) 1928.

8. Hart, D.: *Empyema in Children*, *South. M. J.* 9:823, 1930.

9. Lyon, A. B.: *Bacteriologic Studies of One Hundred and Sixty-Five Cases of Pneumonia and Postpneumonic Empyema in Infants and Children*, *Am. J. Dis. Child.* 23:72 (Jan.) 1922.

10. Menter, M. L.; Bailey, S. F., and DeBone, F. M.: *Pneumonia in Children*, *J. Infect. Dis.* 51:254 (Sept.) 1932.

The two most likely sources of the focus or foci in the lungs are the bronchial tree and the blood stream (the question of lymphatic origin will not be discussed). The information at hand at the present time is inconclusive as to which of these pathways commonly conducts the infection to the lungs, for the difficulties of interpretation are obvious. A staphylococcic abscess of the kidney or of a bone is generally recognized as a metastatic focus, but proof is often lacking. For identical reasons a staphylococcic abscess of the lung can properly be placed in the same category unless evidence exists to prove its origin by aspiration. It may be argued that *Staphylococcus aureus* is to be found in the nasal secretions of normal adults (30 per cent. Nemmann) and that the organism can be isolated frequently from the throat of a normal person as well as from sputum obtained from the bronchi. Aspiration may account for staphylococcic pneumonia, which does not appear to differ appreciably from pneumonia due to other organisms, but it does not explain as readily an isolated abscess or multiple abscesses due to the staphylococcus. On the other hand, the evidence of an embolic (metastatic) origin of the staphylococcic abscess of the lung is sometimes clear. Leaving aside the characteristic miliary abscesses of the lungs occurring during sepsis caused by the staphylococcus, there are not a few instances in which solitary or multiple abscesses of the lung occur in persons who are known to have had staphylococcic bacteremia. A distant source of surface infection, such as paronychia, is the sole evidence in other cases, as in staphylococcic abscess of a kidney or of a bone. In a third group, simultaneous metastatic abscesses in other parts of the body as well as in the lung comprise the evidence for staphylococcic abscess of the lung as a metastatic focus. Finally, the appearance of the pulmonary suppurative lesion at autopsy is quite unlike that of aspiration bronchopneumonia with secondary suppuration.

The embolic origin of many cases of staphylococcic abscess of the lung is stressed for practical rather than for theoretical reasons. The purpose is twofold: first, to indicate that the prognosis is potentially graver in any case of staphylococcic empyema than in a case of the more common pneumococcic empyema because the underlying infection in the lung may be embolic and therefore one of a number of metastatic foci, and, second, to indicate that an appreciation of metastatic origin leads to the conception of an abscess of the lung and not of staphylococcic pneumonia as the pathologic process underlying the empyema. The clinical significance of this view will be shown.

In our series of cases definite portals of entry for general staphylococcic invasion were noted in 22.5 per cent of the children and in 45.5 per cent of the adults. The sites were chiefly active or subsiding skin infections (from a number of which *Staph. aureus* was isolated in pure culture). The histories in this group were often strongly suggestive

of metastatic pulmonopleural lesions rather than of the typical sequence of pneumonia and empyema. In the remaining cases, however, there was little if anything in the history or clinical course to differentiate the staphylococcic from the common pneumococcic infection in the lung and empyema.

In the cases in young infants in our series a history clearly indicative of the metastatic origin of the staphylococcic infection was common. There were 2 striking examples of sepsis of birth, and it is of interest to note that both patients recovered. In 1 infant there were multiple periarticular abscesses at the age of 2 weeks followed shortly thereafter by pyopneumothorax. Dunham's<sup>11</sup> study on sepsis in the new-born confirms our impression that the majority of, if not all, cases of staphylococcic empyema in young infants (which means the great majority of all cases of empyema in young infants, as we have stated) are derived from embolic abscesses of the lungs.

#### PATHOLOGIC PROCESS

In generalized staphylococcic sepsis, empyema secondary to miliary abscesses of the lung is an occasional complication. It rarely requires clinical consideration under such circumstances and is not under discussion in this paper.

The pathologic process in the underlying lung determines the character and the extent of the pleural lesion in staphylococcic empyema. The pulmonary lesions may be single or multiple. The solitary abscess (or group of abscesses) is comparable to the staphylococcic carbuncle of the kidney or the osteomyelitic abscess of the bone. The lesion can properly be termed a "carbuncle of the lung" by analogy to carbuncle of the kidney. The similarity of carbuncle of the kidney, with its cortical involvement, perinephritis and perinephritic abscess, to subpleural carbuncle of the lung, with contiguous sacculated empyema or pyopneumothorax, is evident. In our series all the patients presented suppurative pleuritis at the site of the carbuncle of the lung. Of the 11 adult patients, 5 had sacculated pyopneumothorax at the time of operation, and in 3 bronchial fistulas appeared subsequently as evidence of the rupture of a pulmonary suppurative focus. Of the 31 children, 12 had pyopneumothorax at the time of operation, and bronchial fistulas appeared at a later date in 8 others. Approximately the same percentage in each group gave evidence of the rupture of a pulmonary suppurative focus as the source of the empyema or pyopneumothorax. The data at hand therefore point to an identical process in adults and children. As will be pointed out, however, the clinical manifestations of pleural invasion in children are often different from those in adults.

11. Dunham, E. C.: Septicemia in the New-Born, *Am. J. Dis. Child.* 45:223 (Feb.) 1933.

The pulmonary involvement may not be limited to a solitary abscess or a group of abscesses or to a carbuncle in one lobe. Abscesses may be scattered in more than one lobe or even in both lungs. Occasionally the degree of involvement in children may be so great that a lobe is largely destroyed by the suppurative process. Recurrent pyopneumothorax as the result of successive ruptures of multiple abscesses in the lung occurred in several patients in our series. It is obvious that the mortality in some instances of staphylococcic empyema or pyopneumothorax can be ascribed to the extent and degree of invasion of the lung and not to the pleural infection. This was true in all the cases in our series that came to postmortem examination.

The pathologic process in the pleura depends on the site of the pulmonary focus, its extent and the rate of destruction of the overlying parenchyma. In adults the pleural involvement is usually slow and benign. The empyema or pyopneumothorax develops gradually in encapsulated form. Bronchial communications, when present, are generally insignificant, indicating that the abscess in the lung was probably small and subpleural. Our experience with staphylococcic empyema or pyopneumothorax of adults has been limited, but the architecture has been characteristic in the few cases we have encountered. The collection of pus is in two pockets, with a shelf of infiltrated lung bearing the perforated or nonperforated parenchymal focus lying between them. The encapsulations are dissimilar in size, and the shelf may narrow greatly the communication between them. The surgical significance of this configuration is evident. In our first experience at operation in 1 of these cases the second and larger collection of pus was entirely overlooked after the first had been evacuated and was accidentally revealed beyond a shelf of lung as a result of coughing.

The slow evolution of empyema or pyopneumothorax which has been described as the adult form is also encountered in children. It is not typical of childhood, however, and is less and less frequently seen as the earliest years of life are approached. The characteristic lesion in childhood, and more particularly in infancy, is wide rupture of a staphylococcic abscess of the lung into the pleural cavity. When it evolves slowly, permitting walling-off adhesions to form, pyopneumothorax with little or no displacement of the mediastinum is the result. On the other hand, total pyopneumothorax with great shift of and tension on the mediastinum occurs when the abscess develops rapidly with early rupture. Never present in adults in our series, this picture occurred in one third of the children and in almost all the infants.

#### CLINICAL ASPECTS

The symptoms of staphylococcic pleural infections obviously depend on the pathologic process. Although there may be some overlapping,



four classes of cases can be indicated as follows: (1) sacculated empyema; (2) sacculated pyopneumothorax; (3) total or subtotal empyema with or without mediastinal tension, and (4) total or subtotal pyopneumothorax with or without mediastinal tension.

The first two forms, which we have termed the adult type, can be dismissed at once, for there is nothing in the symptoms to distinguish them from other varieties of empyema. The history comprises the only basis on which the lesions can be suspected to be staphylococcic. As already stated, the history was suggestive of pulmonary metastasis in 45.5 per cent of the adult cases.

The third and fourth varieties, which we have termed the childhood type, present symptoms that range from mild to severe depending on the speed of the accumulation of pus with or without air in the pleural space. The severest cases are those in which the early rupture of the focus in the lung leads to air being blown into the infected pleura with a one way valve action. The shift of the mediastinum is rapidly progressive, with correspondingly increasing tension on the mediastinal structures and embarrassment of the heart and of the opposite lung. The clinical picture is dramatic. The patient is a young child, or more often an infant, who has been ill only a few days. Suddenly there develop severe dyspnea, cyanosis, tachycardia and high fever. Within a few hours the child is in collapse, and death may ensue quickly with the manifestations of asphyxia. When death does not supervene the child remains cyanotic, dyspneic and toxic. Only rarely does gradual compensation for the abrupt shift of the mediastinum occur. There may be an interval of partial relief, followed by a recurrence of the extreme manifestations. On examination the evidences of shift of the heart and of the trachea are found, together with the physical signs of air and fluid in the chest. If mechanical relief is not given, a progressive displacement of the mediastinum will be noted. In other cases empyema or pyopneumothorax has been present for several days with little or no mediastinal tension, and the symptoms have been mild and insignificant. Suddenly the alarming symptoms supervene, and the child presents an urgent problem for relief. Other forms of pulmonary abscesses rupturing into the pleura may present identical clinical pictures, but the occurrence in the early years of life, and particularly in infancy, is distinctive of the staphylococcic lesion. If, in addition, there is a history or clinical course which suggests that the pulmonopleural lesion is metastatic and, of course, if there are other metastatic foci, there should be no doubt as to the staphylococcic origin of the pleural infection.

Among the children in our series were 3 patients who recovered despite the evolution of other metastatic foci. On the other hand, a child who presented no focus other than the pleural one at the time of operation had metastatic lesions subsequently and died with the

picture of sepsis. It may be impossible to evaluate the relative importance of a staphylococcic pleural infection in a child. However, the most important point we wish to make is that, on the basis of our experiences, the lesion should not be considered irremediable unless it is obviously an incidental feature in generalized staphylococcic sepsis.

#### ROENTGENOLOGIC ASPECTS

*In Adults.*—The usual finding has been that of a sacculated collection of fluid or of air and fluid without distortion of the mediastinum. Five of the 11 patients presented well defined collections of fluid. The sacculatum may be lateral, mediastinal, supra-apical or infrapulmonary, depending on the site of the staphylococcic lesion in the lung. A small pyopneumothorax may simulate an abscess of the lung with a large collection of fluid and air. In our experience most sacculated large parietal collections of fluid and air are in the pleura. Accurate roentgenologic localization is essential for correct and efficient drainage. From what has been said it is clear that the roentgenographic picture of staphylococci empyema or of pyopneumothorax in adults is not distinctive.

*In Children.*—The roentgenographic picture is more varied, in keeping with the differences in the pathologic processes in children that have been described. The characteristic feature seen in the roentgenograms of children is a large collection of fluid and air with considerable displacement of the trachea and the mediastinum. The same condition is of course seen in other forms of ruptured abscess of the lung but it is so rarely due to other causes in children (especially in young children and infants) that it can be termed the distinctive feature of staphylococcic pyopneumothorax in the young. A careful inspection of the films will occasionally reveal more or less circular areas of rarefaction or of increased density in the pulmonary field adjacent to the pleural shadows. They represent, respectively, drained or undrained abscesses of the lung. The shadows are pathognomonic of staphylococcic infection under such circumstances, and, when present, offer valuable information regarding the extent of the pathologic process in the lung. Their absence does not, of course indicate an insignificant lesion in the lung, for the shadow of even a large ruptured abscess can be readily obscured by pleural shadows.

When films are taken with the patient lying down, the fluid level may be completely lost and a correct interpretation of the pathologic processes in the pleura and of the changes in the mediastinum may not be possible. It is therefore imperative that all films be taken in the upright posture, even if it is necessary to support the patient. Lateral films are as important as the anteroposterior or postero-anterior views

for the accurate localization of encapsulated effusions. Postoperative films are often necessary for the purpose of checking up or for the determination of a site of retention of pus. These, too, must be taken in the upright posture. The introduction of iodized oil through a sinus in the chest is often of value in the roentgen visualization of residual pockets or of communications between the pleura and the bronchial tree.

#### TREATMENT

*Sacculated Pyothorax or Pyopneumothorax (Adult Type).*—These cases are rarely urgent. The lesion should be localized accurately by physical examination, fluoroscopy and roentgenogram, because entry into the free pleura by aspiration or at operation may convert the encapsulated abscess into total empyema. Sections of one or two ribs are excised for adequate visualization and drainage. After the cavity has been emptied by suction the space is inspected with a sterile light for recesses as well as for the site of rupture. The likelihood of biloculation, as pointed out in the description of the pathologic process, should be borne in mind, and the simple evacuation of a collection of pus should not be regarded as the end of operation until the absence of an additional pocket (or pockets) has been definitely proved. In the 11 cases in adults there was 1 death. The patient had bilateral pulmonary abscesses with multiple pleural encapsulations and died of metastatic staphylococcic abscess of the brain and meningitis. The conclusion that the adult type of staphylococcic pleural infection is a relatively benign lesion not calling for special consideration should not, however, be drawn from our small series of cases. In 2 instances it was necessary to split open the underlying abscess of the lung. Extensive excision of the ribs was required in several cases. Reoperation for additional pockets, probably overlooked at the original operation, has been necessary. We know of instances not included in this series in which chronic staphylococcic abscess of the lung and chronic pleural empyema remained after the primary operations. The operation for staphylococcic empyema or pyopneumothorax should be carefully and thoroughly carried out, with examination for an unruptured subpleural abscess of the lung and drainage of the abscess should one be present. At the end of the operation all recesses are packed with gauze (iodoform) to prevent pocketing. The packings can be left in place for several days, sometimes for a week or longer, and should be replaced only when loosened by discharges.

*Total or Subtotal Empyema or Pyopneumothorax (Childhood Type).*—The minor procedure of closed drainage adequately cares for the acute pathologic process in the pleura, although later revision of the wound is not infrequently required for cure. Open operation in

the presence of an acutely displaced mediastinum is, of course, not to be considered. The important point is that open operation is also contra-indicated with little or no displacement of the mediastinum. The basis for this statement is the difference that exists, in our opinion, between staphylococcic and pneumococcic pleural infections. Whereas mediastinal fixation is apt to be present at a relatively early stage of pneumococcic empyema, a similar fibrinopurulent fixating exudate is not to be anticipated at that time in staphylococcic pleuritis. Furthermore, a condition that begins as staphylococcic empyema without mediastinal tension may at any time become one of pyopneumothorax with great mediastinal shift. In a number of our cases closed drainage resulted in the escape of pus with little or no air at first, to be followed later by the sudden discharge of large quantities of air when the abscess of the lung ruptured into the pleura. Severe and possibly fatal mechanical disturbance might have resulted from the rupture of such an abscess into an open wound, whereas respiratory embarrassment was minimal or lacking in the presence of closed drainage.

The arguments advanced in favor of the treatment of empyema by aspiration cannot be applied with justification, in our opinion, to staphylococcic empyema or pyopneumothorax of childhood. The degree of suction employed to evacuate the pus may open a sealed-off bronchial communication or may widen an existing fistula. If the phenomena of mediastinal tension are not present they may be induced, or if present, they may be greatly increased. To indicate that this is not merely a theoretical objection we refer to a case of staphylococcic empyema in a child not in this series (because not operated on) who went into collapse shortly after therapeutic aspiration was performed and died with the picture of respiratory distress. Disaster is courted each time that therapeutic aspiration is performed, and many aspirations would be necessary in the majority of cases in order to achieve a result. Furthermore, treatment by aspiration, whether successful or not, usually means prolonged morbidity, with its invitation to complications. This is a matter of considerable importance in sick patients, particularly in infants. Finally, unsuccessful treatment by aspiration is apt to result in multiple pleural encapsulations or a fixed collapsed lung, with a major surgical problem as the sequel.

Closed drainage is a minor surgical procedure and, as has been stated, it adequately cares for the acute phase of staphylococcic empyema or pyopneumothorax of childhood. The procedure, which can be carried out at the bedside, consists of a stab thoracotomy through a small intercostal incision. A catheter or small rectal tube is introduced a short distance within the chest and is connected with a length of rubber tubing. The end of the tube is placed under water in a glass receptacle set well below the level of the chest. The only feature of the operative

procedure to be stressed is the necessity of a snug fit at the exit of the drain from the wall of the chest. The tube itself or, better, a snug rubber cuff over the tube is securely fixed to the wall of the chest with strips of adhesive tape. Adhesive strips should also approximate the skin about the drain.

The escape of pus (or air and pus) in the underwater drainage is usually profuse for the first twelve to twenty-four hours after operation, gradually diminishing in amount in the succeeding days. With a considerable bronchial communication, however, large amounts of air may be discharged for days. We have already called attention to occasional cases of staphylococcic empyema in which only pus is discharged at first, to be followed, sometimes suddenly, by the escape of air. These are instances in which the underlying abscess of the lung ruptures into the empyema cavity after closed drainage has been established. It is our distinct impression that this accident has favorably influenced the clinical course when it has occurred under such circumstances.

The escape of air from the pleural cavity by way of a bronchial communication should not be confused with the leakage of air along the drainage tube. The latter is the most important complication after closed drainage; the dangers inherent in a sucking wound are too well known to be recapitulated. The chances of leakage along the tube are reduced by a minimal skin incision, the application of a well occluding dressing at the time of operation and meticulous attention to and observation of the drainage system after operation. The child should not be able to pull at the dressings, and alterations in position should not result in traction on the tubing. Sudden changes in the patient's condition, with particular reference to dyspnea and cyanosis, should be reported promptly and should be as promptly investigated. They may be referable to a sucking wound or to obstruction of the drainage. The former is cared for by the introduction of a larger tube with strips of gauze packed between it and the edge of the incision in the soft parts. The arrest of a steady flow of pus in the first week after operation generally means plugging of the tube, which can usually be overcome by aspiration or by angulation of the tube, for which replacement may be necessary. We wish to emphasize our observation that the complete or almost complete cessation of flow of pus in the first days after operation has always meant retention of pus within the chest and not a premature cure of the empyema.

The nursing staff should receive instruction for appropriate action in the event of one of two accidents that may occur in closed drainage. One is the escape of the end of the tube from beneath the water level. The tube should be clamped off (a clamp is kept at the bedside in all cases of closed drainage) and then reinserted into the water that is in

a receptacle situated well below the level of the chest. An additional piece of tubing can be attached by means of a glass connection. The second accident is a sucking wound following the escape of the tube from the wound in the chest. All dressings should be removed by the nurse unless a physician is immediately available, and the lips of the wound should be approximated until a tube can be reinserted. In our service, calibrated glass urinals are used as the receptacles for closed drainage. The amount of drainage is measured and recorded daily. The urinal is then emptied and a measured amount of water introduced. The tube is clamped off by the nurse before the change is made. The clamp is not removed until the end of the tubing is in place below the surface of the water. We have given some space to the nursing in cases of closed drainage because correct appreciation by the nurse of the problems involved may be vital in an emergency.

The duration of efficient closed drainage varies. In some cases the intercostal drain becomes loose in a few days, and pus leaks along the tube. The drainage remains truly closed for an average of one week. After from seven to ten days, at which time the discharge of pus is usually slight, the mediastinum is probably more or less fixed. The tube can then safely be removed, to be replaced by a tube for open drainage. Revision of drainage by the excision of a portion of a rib is often necessary; it was done in 60 per cent of our cases.

The frequency of bronchial communication has already been pointed out. Of the 11 adults 5 had bronchial fistulas at the time of the operation and 3 presented fistulas subsequently. Of the 31 children, pyopneumothorax at the time of closed drainage existed in 12, and bronchial communication appeared subsequently in 8. An actual or potential bronchial communication must therefore be assumed to be part of the picture in most cases of staphylococcic pleural infection. Accordingly, irrigation of the pleural cavity is absolutely contraindicated in the post-operative treatment. In none of our cases has the bronchial fistula been a special problem of management. Adequate drainage has meant early expansion of the lung, with spontaneous closure of the fistula as the result. The fistulas healed in all the patients and remained closed as determined by the follow-up.

#### GENERAL TREATMENT

The administration of oxygen with or without the admixture of carbon dioxide may save a life during the stage of acute tension. A slow intravenous drip of a 5 per cent solution of dextrose and physiologic solution of sodium chloride is invaluable in the treatment of the circulatory collapse that is so often present in the severe cases in infancy. It was maintained for many days in

several cases in our series and was, in our opinion, the decisive factor in the recovery of the patients after adequate drainage was instituted. That adequate drainage is essential for desperately sick infants should be stressed. There is a current impression that infants in such a condition do not withstand operative procedure and therefore that the less done the better. Our experience has been that prompt and adequate drainage of the suppurative focus has given them their chance for recovery. Residual pockets after primary closed drainage must be more carefully watched for than in infants or in children who are not desperately ill and must be more promptly evacuated when found. The recovery of several children in our series can properly be ascribed to active surgical treatment combined with constant supervision by the physicians of the pediatric service. Staphylococcic empyema or pyopneumothorax should be treated only in the hospital, and the patient should receive there the constant vigilance of the nursing, pediatric and surgical staffs.

#### COMPLICATIONS AND MORTALITY

There was 1 death from cerebral metastasis among the 11 adults, to which reference has already been made. In another patient the blood culture was positive after drainage of the empyema, but additional metastatic foci did not appear, and the patient recovered. A metastatic abscess in a kidney developed in a third patient. Complications were much commoner in children. Of the 31 children, 10 presented other metastatic foci, chiefly lesions of the bones and joints and abscesses in the soft parts. There were 13 deaths (mortality, 42 per cent). Almost exactly half of the children were under 1 year of age, and the mortality in the group of infants was 52.5 per cent. Autopsies were performed following 6 of the 13 deaths. The summary of the protocols is the best index of the gravity of staphylococcic pleural infections in childhood: (1) suppurative pulmonary focus and empyema on the opposite side; (2) suppurative pericarditis; (3) suppurative pulmonary focus and suppurative pleuritis on the opposite side and fibrinopurulent pericarditis; (4) multiple abscesses in the opposite lung; (5) multiple perforations of abscesses of the lung and pericarditis with serous effusion, and (6) multiple perforations of abscesses of the lung and fibrinopurulent pericarditis.

The comparative mortality in children in Mount Sinai Hospital with the other varieties of pleural infection for the same years (from 1928 to 1932) as those for which the staphylococcic infections have been reported is worthy of note. The other infections comprised the pneumococcic, streptococcic and anaerobic forms. There were no deaths from pneumococcic empyema or pyopneumothorax. In the group with streptococcic involvement the mortality from empyema was 15 per cent and from pyopneumothorax 25 per cent. The mortality from anaerobic

empyema (ruptured putrid abscess of the lung) was 30 per cent. These comparative figures offer further evidence that the staphylococcic infections of the pleura should not be classified with the other pleural infections but should be considered separately because of their gravity or potential gravity. This feature should be added to those we have described as distinctive in the etiology, pathology, clinical manifestations and treatment of staphylococcic pulmonopleural infections. The mortality depends, then, on the dissemination of staphylococcic foci. There should be no appreciable mortality from staphylococcic empyema or pyopneumothorax secondary to a solitary abscess of the lung when rationally conceived therapy has been employed.

#### SUMMARY

Staphylococcic empyema or pyopneumothorax is a definite entity, with distinctive features in etiology, pathology, clinical manifestations, treatment and mortality.

The staphylococcus is the cause of the great majority of suppurative pleural infections in infants.

The pulmonary lesion from which the staphylococcic pleural infection is derived is usually an abscess of the lung. The invasion of the pleura is by rupture of the abscess in the majority of cases.

The evidence is often clear that a staphylococcic abscess of the lung with its complicating pleural infection is a metastatic lesion. Abscesses of the lung, with or without accompanying empyema, may be multiple and bilateral. The solitary abscess is analogous in origin and in pathologic process to carbuncle of the kidney and can be termed carbuncle of the lung.

Four clinical groups are described: sacculated empyema, sacculated pyopneumothorax, total or subtotal empyema with or without mediastinal tension and total or subtotal pyopneumothorax with or without mediastinal tension. Communications with bronchi are present in the majority of cases in each group.

The first two varieties, termed the adult type, present distinguishing pathologic features but are not distinctive clinically.

The third and fourth varieties, termed the childhood type, are characterized by severe mechanical disturbances (dyspnea, cyanosis and tachycardia) if there is tension on and shift of the mediastinum. The lesion which requires relief most urgently occurs with early rupture of the abscess of the lung in infants or in young children.

Distinctive roentgenologic features of the childhood type are described.

The treatment of the adult type, rarely urgent, is by complete opening of the empyema through a liberal incision. The underlying abscess of the lung may require drainage.



Urgent treatment is often imperative for the childhood type. Closed drainage is employed, and the reasons therefor are given. Treatment by aspiration is unjustifiable for the reasons given.

The treatment by closed drainage is given in detail.

The general principles of treatment are stated.

The complications and mortality are described.

## REACTIONS OF CONTENTS OF JEJUNUM AND EXPERIMENTAL PRODUCTION OF PEPTIC ULCER

\*PATRICK P. T. WU, M.D.

Fellow in Experimental Surgery, the Mayo Foundation  
ROCHESTER, MINN.

The clinician has believed for many years that in some way acid is a factor in the production of peptic ulcer. Many facts tend to confirm this belief. The most important of these facts are the following: 1. The typical lesion that is called peptic ulcer occurs only in that portion of the gastro-intestinal tract that can be exposed to an acid medium. 2. Many patients with peptic ulcer have a so-called hyperacid condition. 3. A definite relationship exists between some of the symptoms of the condition, such as pain after meals, and the activities of the stomach, including its secretory function. 4. In many instances the taking of food that will act as a buffer against acid or of medicinal agents that will neutralize acid gives relief from pain.

Much of the recent experimental work on peptic ulcer also has tended to emphasize the great importance of acid as a factor in the development of peptic ulcer. Exalto<sup>1</sup> appears to have been the first to conclude from experimental investigation that jejunal ulcers develop after gastrojejunostomy as a result of the influence of the acid gastric juice on the intestinal mucous membrane. Mann and Williamson<sup>2</sup> drained the secretions that passed into the duodenum away from the point of emergence of the gastric contents and substituted the jejunum for the duodenum in relation to the stomach. Lesions which both grossly and microscopically resembled peptic ulcers as seen in man developed in the transposed jejunum in most of the animals on which this operation was performed. Thus, a method was developed which made possible the experimental study of peptic ulcer. The results of the work of Mann and Williamson have been repeatedly corroborated and greatly added to

---

This work was done at the Institute of Experimental Medicine, the Mayo Clinic, Rochester, Minn. The author now lives in Shanghai, China.

1. Exalto, J.: *Ulcus jejuni nach Gastroenterostomie*, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **23**:13, 1911.

2. Mann, F. C., and Williamson, C. S.: *The Experimental Production of Peptic Ulcer*, Ann. Surg. **77**:409 (April) 1923.

on by other investigators, namely, Matthews and Dragstedt,<sup>3</sup> Morton,<sup>4</sup> McCann,<sup>5</sup> Mann and Bollman,<sup>6</sup> Weiss,<sup>7</sup> Neuman and others.<sup>8</sup>

Mann and Bollman<sup>6</sup> developed a method of securing gastro-intestinal contents from any portion of the gastro-intestinal tract by anastomosing an isolated loop of intestine to the site of the tract from which it was desired to remove the contents, and by draining the contents through the transposed loop to the outside of the body.

With the development of methods for the experimental production of peptic ulcer and for the repeated securing, under physiologic conditions, of specimens of the contents at various levels of the gastro-intestinal tract, it became possible to study the changes that occur in the reaction of the contents that pass over the ulcer-bearing area before, during and after the development of the ulcer. The purpose of this study was to determine the reaction of the contents of the jejunum before and after an operation which is usually followed by the formation of a typical peptic ulcer of the jejunum.

#### EXPERIMENTAL PROCEDURE

Five different experiments were carried out. The variations in the reaction of the jejunal contents during fasting and following a test meal were observed both before and after an operation to produce peptic ulcer. All of the operations were performed with a sterile technic on healthy normal dogs that had fasted for from eighteen to twenty-four hours; the animals were anesthetized with ether. No clamps were applied to the intestines at any time. The anastomoses were made with two layers of no. 00 twenty day chromic catgut.

The essentials of the surgical procedures were as follows: 1. A jejunal fistula was prepared by resecting from the ileum a loop from 12 to 18 cm. in length, from 30 to 50 cm. from the cecum. The continuity of the ileum was restored by an end-to-end anastomosis. The distal end of the isolated segment was anastomosed,

3. Matthews, W. B., and Dragstedt, L. R.: The Etiology of Gastric and Duodenal Ulcer, *Surg., Gynec. & Obst.* **55**:265 (Sept.) 1932.

4. Morton, C. B.: Observations on Peptic Ulcer: V. Findings in Experimentally Produced Peptic Ulcer: Etiologic and Therapeutic Considerations, *Ann. Surg.* **87**:401 (March) 1928.

5. McCann, J. C.: Experimental Peptic Ulcer, *Arch. Surg.* **19**:600 (Oct.) 1929.

6. Mann, F. C., and Bollman, J. L.: Experimentally Produced Peptic Ulcers: Development and Treatment, *J. A. M. A.* **99**:1576 (Nov. 5) 1932.

7. Weiss, A. G.: Ulcères chroniques gastro-duodénaux expérimentaux créés par la dérivation des sucs alcalins duodénaux, *Strasbourg-méd.* **90**:549 (Sept. 15) 1930.

8. Neuman, F.; Demoor, P., and Deloyers, L.: Contribution à l'étude de la pathogénie des ulcères gastro-duodénaux. Dérivation totale des sucs duodénaux, biliaires et pancréatiques dans l'iléon terminal, *Compt. rend. Soc. de biol.* **105**:887 (Jan. 8) 1931.

9. Mann, F. C., and Bollman, J. L.: The Reaction of the Content of the Gastro-Intestinal Tract, *J. A. M. A.* **95**:1722 (Dec. 6) 1930.

end to side, to the jejunum from 5 to 10 cm. below the ligament of Treitz; the proximal end was brought out through a stab wound on the anterior abdominal wall and fixed separately to the muscles, and to the skin. 2. For the production of jejunal ulcer the pylorus was isolated and sectioned, the duodenal end was closed and inverted and the jejunum was divided a short distance above the internal stoma of the previously made fistula. The distal end of the jejunum was anastomosed, end to end, to the pyloric portion of the stomach. The proximal end of the jejunum was anastomosed, end to side, to the terminal portion of the ileum not more than 30 cm. from the cecum.

For the first three days after each operation nourishment was provided daily by two intravenous infusions of a 10 per cent solution of dextrose in physiologic solution of sodium chloride, the amount being 10 cc. per kilogram of body weight. Then for a week the animals were fed only milk, syrup and water. Subsequently, they were maintained on a diet consisting of biscuits, milk, syrup and water with an occasional allowance of lean horse meat. No coarse food was given.

The animals regained their normal state of health about ten days after the first operation. After a brief period of training, each dog would lie quietly on its side while a specimen was being withdrawn. On each dog, two or three series of analyses of the jejunal contents were made each week, making a total of seventy-seven tests. Food was withheld for from eighteen to twenty-four hours before each test. Samples were withdrawn every fifteen minutes by means of a rubber catheter inserted through the transposed loop. The test meal consisted of 10 cc. of milk for each kilogram of body weight. The reaction of the jejunal contents was studied for half an hour with the animal fasting and then for two and one-half hours after the animal was fed. The hydrogen ion concentration of the samples was determined with the quinhydrone gold electrode and the Leeds and Northrup potentiometer. If any trace of blood was present, the results were discarded. A total of nine hundred and twenty-four determinations were made.

## RESULTS

The results of the experiments were definite (tables 1 and 2). In normal animals the reaction of the jejunal contents in the fasting state was usually found to be a  $p_H$  of from 7.6 to 8.1. It was never more alkaline than  $p_H$  8.3 or more acid than  $p_H$  6.91. The range of fluctuations during the intervals of fifteen minutes was between a  $p_H$  of 0.06 and of 0.41, with an average of 0.26, but it was observed occasionally to vary from 0 to 0.83.

After feeding the reaction became more acid by an increase of the  $p_H$  of from 1.05 to 1.46, with an average of 1.3. The  $p_H$  was found to be about 7 or 7.8, with occasional variations to 8.28 and 5.22 as the extremes. The excursions in reaction occurred usually within a range of  $p_H$  between 1.09 and 1.8, with an average of 1.48. The widest range of excursion in  $p_H$  observed was 2.64 and the narrowest range, 0.77.

After the usual values and the variations in the reaction of the jejunal contents had been determined in a normal dog, an operation for duodenal drainage was performed. Shortly afterward each animal began to show a progressive loss in weight and a gradual increase in weakness. The periods between the time of the last operation and the

TABLE 1.—Range of  $pH$  of Jejunal Contents Before and After a Test Meal of Milk and an Operation to Produce Ulcer

Dog		Reactions Before and After Test Meal											
		Minutes Before		Minutes After									
		30	15	15	30	45	60	75	90	105	120	135	150
1	Normal.....	8.15	8.15	7.67	7.62	7.14	7.89	7.72	7.93	7.45	8.05	8.00	8.08
	Greatest.....	5.09	4.56	5.35	7.77	2.52	6.29	3.00	6.98	3.11	2.49	2.50	2.90
	Least.....	7.10	7.79	7.02	5.90	5.78	5.85	5.13	6.64	6.42	7.89	8.00	8.10
2	Normal.....	7.94	8.03	6.03	6.52	6.05	6.03	6.24	8.10	7.29	7.31	7.05	7.66
	Greatest.....	3.04	4.21	5.04	4.57	4.37	5.09	4.11	3.30	3.80	4.64	3.75	2.18
	Least.....	6.37	6.44	6.32	6.20	6.02	7.08	7.89	6.27	6.39	6.20	6.10	6.37
3	Normal.....	7.49	7.54	5.78	6.29	6.17	6.00	6.81	6.05	7.56	7.64	7.00	7.19
	Greatest.....	7.22	8.11	5.95	4.97	4.19	5.93	6.71	4.15	5.56	5.58	2.02	5.07
	Least.....	5.86	5.81	4.26	3.98	6.22	6.69	4.64	4.58	7.66	7.12	7.98	7.34
4	Normal.....	7.84	7.88	7.56	7.31	6.71	7.17	6.49	7.56	7.98	7.77	7.98	8.03
	Greatest.....	8.10	7.96	5.59	6.69	7.79	7.66	8.10	8.08	7.27	7.93	7.88	4.80
	Least.....	7.72	7.74	7.00	6.89	6.31	7.56	6.78	7.49	7.19	6.41	7.08	7.81
5	Normal.....	7.64	8.10	8.10	7.81	7.93	8.03	7.72	7.37	7.59	7.00	7.79	7.91
	Greatest.....	6.86	7.44	4.49	6.49	5.74	7.13	7.76	5.63	5.47	4.09	2.85	6.54
	Least.....	7.10	7.83	6.74	6.81	6.64	6.39	6.63	6.41	6.03	6.73	6.49	6.95

\* Three tests were made on each dog. The normal range represents the changes in  $pH$  of the jejunal contents before and after a test meal in normal animals; the greatest and least range, the greatest and least amount of change in  $pH$  of the jejunal contents (during fasting and after a test meal) after operation to produce ulcer and when, in some instances, an ulcer was actually developing.

TABLE 2.—Comparative Data Showing that the Jejunal Contents Were Constantly More Acid After Operation to Produce Ulcers and While Ulcers Were Developing

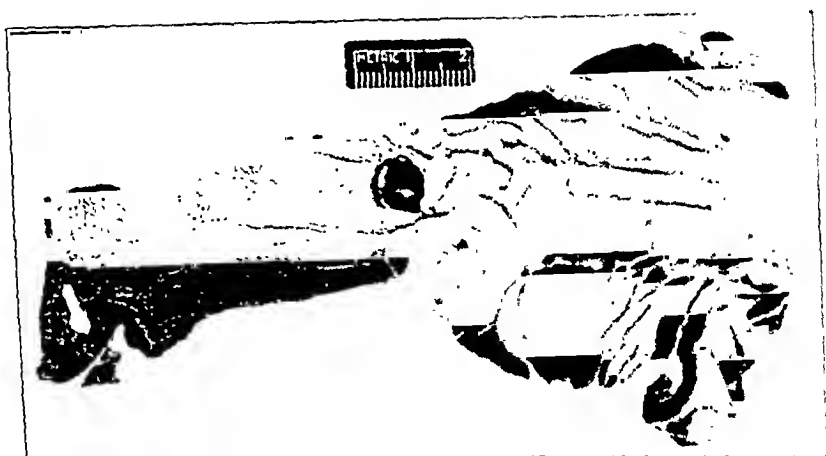
Reaction of Jejunal Contents		Operation	
		Before	After
When fasting			
$pH$ .....		7.6 to 8.1	5.5 to 7.9
Range of fluctuations in $pH$ .....		0.06 to 0.41	0.14 to 1.33
After feeding			
$pH$ .....		7.0 to 7.8	5.2 to 6.9
Range of fluctuations in $pH$ .....		1.09 to 1.80	1.93 to 4.26

TABLE 3.—Period of Survival After Operation, Together with Necropsy Data

Dog	Date of Drainage Operation	Date of Death	Period of Survival, Dnys	Type of Ulcer
1	5/10/31	7/24/31	75	Perforating chronic ulcer, 1 by 1.5 by 0.2 cm., on posterior wall of jejunum just distal to pylorus; the base was adherent to duodenal stump and to greater omentum
2	6/ 3/31	7/ 8/31	33	Chronic ulcer, 1 by 0.5 by 0.2 cm., on anterior wall of jejunum just distal to pylorus; several areas of erosion were present on mucosa of pyloric portion of stomach
3	2/27/31	4/11/33	41	Chronic ulcer, 2.5 by 1.2 by 0.3 cm., on posterior wall of jejunum just distal to pylorus; subacute ulcer, 1 by 0.8 by 0.1 cm., on anterior wall of jejunum about 3.5 cm. from pylorus
4	3/ 6/33	3/31/33	23	Perforated chronic ulcer, 1 by 1 by 0.2 cm., on right posterior wall of jejunum just distal to pylorus
5	3/ 8/33	4/ 9/33	32	Chronic ulcer, 2 by 0.8 by 0.2 cm., on posterior wall of jejunum just distal to pylorus; area of erosion, 5 mm. in diameter, on mucosa of pyloric portion of stomach

time of the animal's death were twenty-three, thirty-two, thirty-three, forty-one and seventy-five days, respectively. At necropsy a chronic ulcer was found in each instance and it was almost always situated on the posterior wall of the jejunum just distal to the gastrojejunal stoma. The dimensions of the craters varied markedly. One of the ulcers (figure) had perforated, and the base of another was adherent to the duodenal stump and to the greater omentum. In one case a "kissing ulcer" was present simultaneously, whereas in two other cases there were areas of erosion of the mucosa of the pyloric portion of the stomach (table 3).

In the same animals, after surgical drainage of the duodenum, the reaction of the jejunal contents in the fasting state was observed to be



Photograph of specimen obtained at necropsy twenty-three days after surgical drainage of the duodenum. The stomach is on the right and the jejunum on the left. The probe indicates the location of the internal stoma of the jejunal fistula.

usually a  $p_H$  of from 5.5 to 7.9, with values of 2.44 and of 8.32 as the extreme variations. Within fifteen minutes the readings revealed a difference of from 0.14 to 1.33, with an average  $p_H$  of 0.85. The greatest amount of oscillation was 5.21 and the least, 0.02.

Rapid fluctuations occurred following a meal of milk. The  $p_H$  value showed a reduction from the fasting level of from 1.4 to 3.6, with an average decrease of 2.2. The reaction ranged from  $p_H$  5.2 to 6.9. At times an alkalinity of  $p_H$  8.33 or an acidity of  $p_H$  1.71 was noted. The most acid reaction was found either when the animal was fasting or at some time after feeding. The range of fluctuations in  $p_H$  was between 1.93 and 4.26, with an average of 2.87. Occasionally as much variation in reaction as 5.53 or as little as 0.74 were observed.

## COMMENT

The purpose of making this investigation was to answer the following questions: 1. Are there any changes in the reaction of the jejunal contents after they pass over the ulcer-bearing region of the jejunum before and after an operation that almost invariably is followed by the development of a peptic ulcer? 2. Are there any significant changes in the reaction of the jejunal contents preceding, during or after the development of a jejunal ulcer?

Concerning the answer to the first question, the results were definite. In these experiments the jejunal contents which were propelled over the site where the ulcer developed were definitely more acid than normal. It was also found that the fluctuations in reaction both in the fasting state and after feeding were much wider after the operation for the production of ulcer. It is justifiable to conclude, therefore, that the ulcer developed in a mucosa exposed not only to a more acid medium but to one in which the fluctuations of acidity were greater than normal.

It was not possible to obtain a definite answer to the second question because of the impossibility of determining the exact time at which an ulcer began to develop. However, a sufficient number of tests were made during the period of survival after the last operation so that if a significant change in acidity had occurred it would have been observed in some of the animals. Although the difference in the reaction of the jejunal contents before and after the operation for producing ulcers was definite, no significant change was noted in the reaction of the jejunal contents immediately after operation and later when an ulcer either was developing or had developed. In these experiments there did not appear to be any change in acidity that would indicate the time at which the ulcer began to develop, nor did the reaction of the jejunal contents change after the ulcer was actually present.

## SUMMARY

Experiments were performed to determine the reaction of the jejunal contents in fasting animals and in the same animals after a test meal, both before and after an operation was performed for the production of jejunal ulcer. It was found that the mucosa of the jejunum in the ulcer-bearing region is exposed to contents that not only are more acid than normal but show a much wider range of fluctuations in reaction both in the fasting state and after feeding. No definite changes in the hydrogen ion concentration of the jejunal contents were noted preceding, accompanying or following the development of an ulcer.

# TUBERCULOSIS OF A DIAPHYSIS

## REPORT OF A CASE

GEORGE E. BENNETT, M.D.

AND

H. ALVAN JONES, M.D.

BALTIMORE

While there have been numerous reports of cases of tuberculous lesions of the diaphysis of a long bone in the German and French literature, references to such lesions in the American journals have been rare. It is because of the comparatively few reports found in the American literature and because of the extreme difficulty in the differential diagnosis that we have been prompted to report the occurrence of a fulminating type of diaphyseal tuberculosis that remained unrecognized prior to the postmortem examination.

## REPORT OF CASE

*History.*—A colored man, aged 22, was first seen in the outpatient department on April 13, 1932, complaining of pain in the left knee.

The family history was unimportant. The patient's general health had always been good, and he had had no acute illnesses except an attack of grip in December 1931, at which time he was ill for about four weeks. He frequently had colds in the chest during the winter months, and on several occasions he expectorated blood. He said that he had never had a venereal disease. He had undergone no operations.

He had had pain in the left knee for four days, sudden in onset and initiated following a misstep on descending a flight of stairs. There had been no swelling of the knee and no subjective fever or chills. The pain was worse at night—severe enough to keep him awake—and he stated that he had had sweats at night during the past three weeks. He had lost about 12 pounds (5.4 Kg.) in weight during the two months preceding admission. He had no cough, and the other systems were normal.

On examination the patient was found to be a well developed and fairly well nourished young colored man. The examination gave negative results, except for pain in the left thigh on abduction of the leg. Roentgenograms of the hips and pelvis revealed no abnormalities. The Wassermann test of the blood was negative. The patient was given salicylates and advised to apply heat locally. He returned to the dispensary at weekly intervals until May 4, when examination revealed an indurated, tender and fusiform swelling in the middle third of the left thigh, with a palpable thickening of the midportion of the shaft of the femur. The temperature was 100 F., and the pulse rate, 110. Roentgen examination revealed forma-

---

From the Department of Surgery, Division of Orthopedic Surgery, Johns Hopkins Hospital.

The pathologic material was obtained through the courtesy of the Department of Pathology.



tion of periosteal new bone, beneath which there were several small areas of destruction in the cortex (fig. 1). A roentgen examination of the chest showed an old, thickened pleura at the base of the right lung.

*Clinical Course.*—The patient was admitted to the hospital on May 4. Physical examination revealed nothing in addition to the conditions previously noted. The blood showed 8,160 white cells, with 78 per cent polymorphonuclears and 78 per cent hemoglobin. Urinalysis revealed nothing of importance. On the evening of the day of admission, the temperature rose to 104 F. (rectal). On the following day an exploration of the region of the middle third of the left femur was made, and at the site of enlargement some boggy, purplish granulation tissue was found over the anterior and lateral aspects of the shaft. There was no free pus, and a smear made at that time showed no organisms. A culture and a section of bone and granulation tissue were obtained. Frozen section showed granulation tissue in which new blood vessels and fibrosis predominated. There was no infiltration of round cells to bear out the presence of infection and no proliferating tissue suggesting a tumor. The bone was not drilled because the operator thought that the lesion grossly suggested sarcoma, though the sections were suggestive of a subacute osteomyelitis; the wound was closed without drainage.



Fig. 1.—Roentgenogram of the left femur, showing destruction of the sub-cortical and medullary bone with proliferation of the periosteal bone in the mid-shaft.

Within twenty-four hours the culture was reported as showing *Staphylococcus aureus*. Because of this report and the report on the frozen section, on the day following the operation the wound was opened and treatment with maggots instituted. After eleven weeks the wound healed, and the patient was discharged from the hospital on July 20. During the period of hospitalization, the patient continued to have fever, the temperature ranging from 99 to 102 F. even until the time of his discharge; but nothing could be found to explain this occurrence except that the roentgenograms taken at intervals of from three to four weeks showed an increasing destruction of the middle third of the shaft of the femur with considerable new formation of bone, despite the healing of the soft tissues (fig. 2).

Twelve days following his discharge from the hospital, the patient returned to the dispensary complaining again of considerable pain in the left thigh, and on examination a fluctuant swelling was found beneath the healed scar on the lateral aspect of the midthigh. The patient was readmitted to the hospital on August 5. His temperature on admission was 104 F. The leukocyte count was 7,200. At operation on August 8, about 60 cc. of brownish, semipurulent material was obtained. The exposed bone was found to be thickened and "moth-eaten" in appearance. A large portion of the lateral wall of the cortex in the midshaft was removed and the medullary cavity exposed. No sequestrums were found. Micro-

scopic examination of the operative specimen revealed a chronic inflammatory process. Treatment with maggots was again instituted for a period of eight weeks, with no improvement locally or generally, and an unremitting, hectic type of fever continued throughout this period. Cultures of the blood repeatedly gave negative results; urinalysis revealed nothing abnormal, and the hemoglobin dropped to 67 per cent. A large abscess developed at about this time over the medial aspect of the middle third of the thigh. Although the wound over the outer aspect of the thigh remained wide open, it was felt that the femur was not being adequately

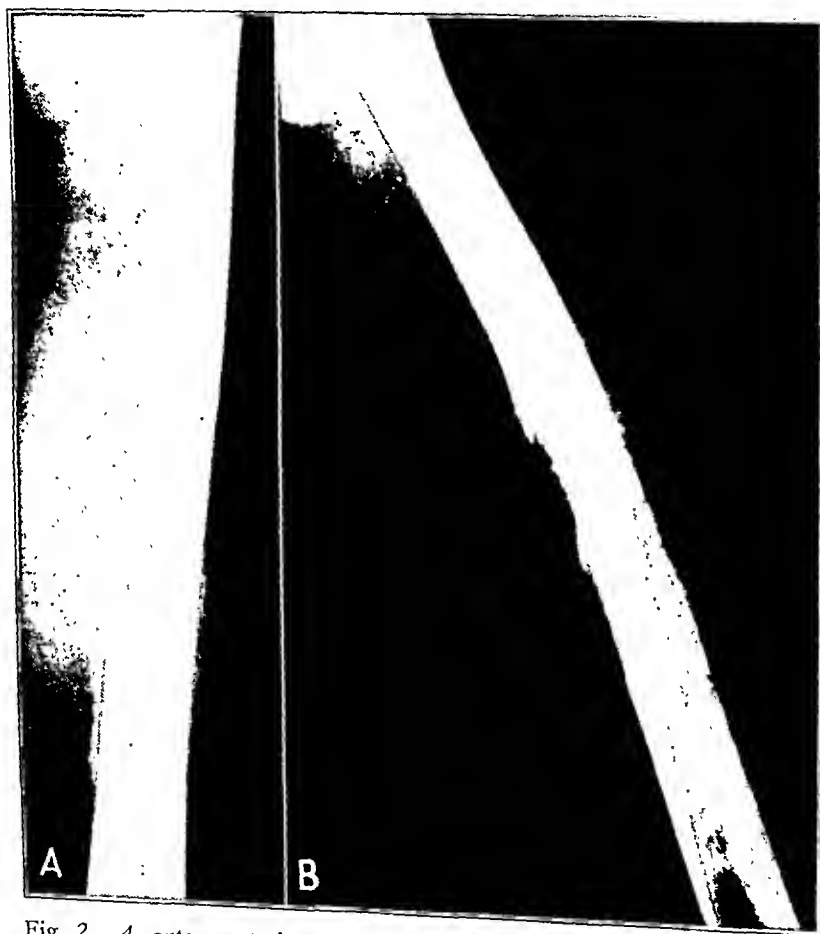


Fig. 2.—*A*, anteroposterior, and *B*, lateral, roentgenogram of the left femur, showing an increasing amount of destruction of the shaft, with considerable formation of new bone.

drained, and on October 6, at operation, the abscess cavity was evacuated, and an extensive saucerization of the upper two thirds of the femur was performed. At this time the peculiar character of the lesion was especially noted, for there were numerous multilocular, small cavities of bone filled with a brownish granulation tissue, and the bone was eburnated and laminated. No sequestra were found. Microscopic examination of the operative specimen revealed a dense bone with considerable fibrous tissue in the lacunae. The cortical bone was curiously dis-

torted, the usual spicules being replaced by a labyrinth formation. Granulation tissue was noted in the marrow spaces. No tubercles were seen (fig. 3).

Following this operation there was a rapid, down-hill course. The patient's hectic fever remained unaltered, and repeated blood transfusions gave only a temporary general relief. Early in November a cough developed, and while clinically the examination of the chest showed nothing abnormal except an old, thickened pleura at the base of the right lung, roentgenograms revealed a beginning infiltration of both apices. On November 27 the patient suddenly became unconscious and had five convulsive seizures at intervals of about one hour, with



Fig. 3.—*A*, roentgenogram of the left femur made at the time of the last operation, showing the numerous cavities of the small bone and sclerosis of the bone. *B*, roentgenogram of the left femur made six weeks prior to that shown in *A*, depicting more clearly the multiple cyst and the peculiar labyrinth formation within the bone.

involvement of the left side of the face and the right arm and leg. After eight hours, he regained consciousness, and though stuporous for another twenty-four hours, he remained free from symptoms suggestive of an intracranial lesion until December 25, when he began to complain of severe headaches with occasional vomiting. Examination revealed beginning choked disks and a Kernig sign on the right, and spinal puncture gave fluid under increased tension containing 300 cells per cubic millimeter. When cultured, the fluid was sterile. An injection of air

showed that the right ventricle was slightly irregular in outline. The patient gradually became comatose and incontinent; marked spasticity of the extremities and edema of the eyelids developed, and he died on Jan. 5, 1933.

*Macroscopic Postmortem Examination.*—The lungs were densely adherent to the parietal pleura and showed rather extensive tuberculosis, particularly in the upper lobe of the left lung, where, anteriorly and about 6 cm. from the apex, there was a cavity 3 cm. in diameter, with a tough, caseous lining. The peribronchial and mediastinal glands contained yellow, caseous tubercles but no calcification. Scattered tubercles were found in the spleen, kidneys and liver. Minute military tubercles were not seen. The brain showed tuberculous meningitis, rather marked over the dorsal surface of each hemisphere and particularly severe on the left side. Two rather large tubercles, one 8 mm. and the other 4 mm. in diameter, well encapsulated, were found within the brain substance, in the left parieto-occipital region. On the medial surface of the left hemisphere just above the corpus callosum was a caseous mass which extended to the meninges. On further section it appeared that all of these caseous masses were part of one irregular nodule.

The left femur showed an extensive lesion involving the middle portion of the bone, beginning 10 cm. from the head of the bone and extending to within 12 cm.

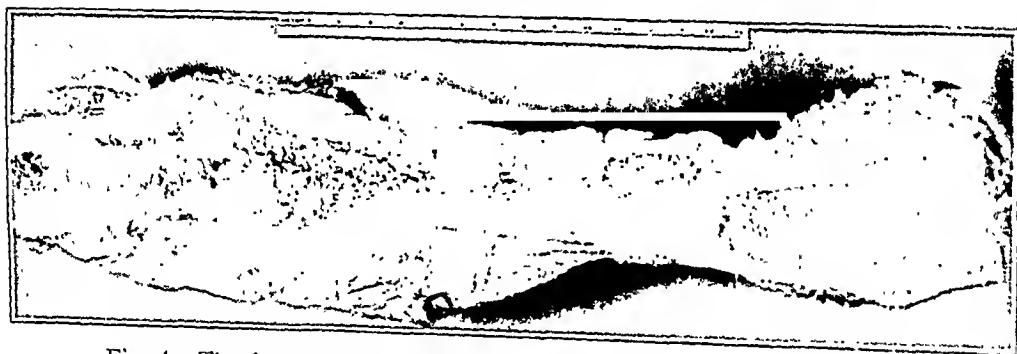


Fig. 4.—The femur grossly, after division through its longitudinal axis.

of the knee joint. The greater part of the middle of the shaft was destroyed, with a layer of bone along the medial aspect about 1 cm. in thickness and suggestive of new bone formation. The lower part of the shaft could be seen protruding into a large central cavity. This cavity was about 10 cm. in length and 3 cm. in width, with formation of new bone about it. The cavity was lined by a yellowish, opaque, caseous layer about 1 mm. in thickness. Above the cavity there were extensive induration and thickening of the periosteal tissue. When the bone was split longitudinally, there were many eroded areas within the shaft, and several sinuses ran through the new-formed bone communicating with abscess cavities within the bone and without (fig. 4).

*Microscopic Postmortem Examination.*—There were some old tubercles in the lungs, but there were also large areas of caseous pneumonia. Tubercles were found, as mentioned in the report on the macroscopic examination, in the liver, spleen and kidneys. Fresh caseous tubercles were found in the meninges and in the brain substance in the occipital region. In the left femur, the sections showed that the marrow was fatty, though there were a few islands of blood formation. The bone was dense, and within the canals there were fibrous tissue and granulation tissue. The granulation tissue contained many tubercles. Tubercles were also found in the granulation tissue taken from the operative wound and in material from the



Fig. 5.—Photomicrograph of a postmortem specimen of the left femur. The section shows granulation tissue, a little caseation and several tubercles.

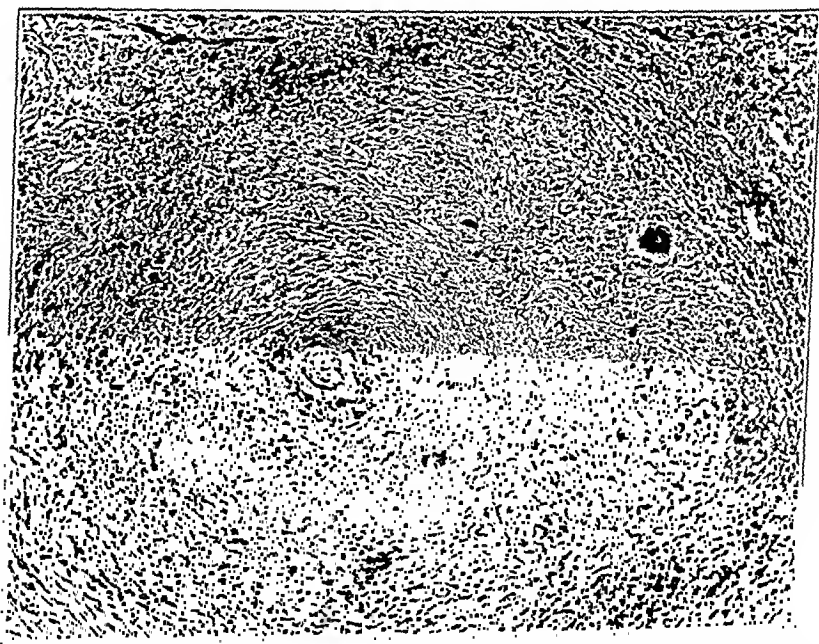


Fig. 6.—Photomicrograph of a section of the material from the wound at autopsy, showing a typical tubercle.

draining sinus over the medial aspect of the leg. There were a few small tubercles which appeared to be rather hard; they were seen in a section made from a lymph gland taken from the left groin (figs. 5 and 6).

## COMMENT

Tuberculosis of the diaphysis of a long bone is exceedingly difficult, almost impossible, to differentiate roentgenographically from a similar lesion produced by syphilis or a malignant process. This difficulty was especially emphasized by Lovett and Wolbach<sup>1</sup> in 1920 and by Bromer and Downs<sup>2</sup> in 1933. A study of the roentgenogram reproduced in figure 1 illustrates the difficulty in a differentiation between subacute osteomyelitis and sarcoma. Against osteogenic sarcoma are the nature of the periosteal reaction and the extension and also the localization of the destruction of the bone immediately beneath the cortex. However, such a lesion is suggestive of Ewing's tumor.

Clinically, we knew that we were dealing with an obscure type of lesion, but, unfortunately, because we did not suspect tuberculosis, the usual laboratory procedures of inoculation of guinea-pigs and staining of sections for tubercle bacilli were not carried out. Moreover, the pathologists found no suggestion of tuberculosis from the many operative specimens. The tuberculous character of the lesion was not demonstrated until the postmortem examination, when the lesion of the femur suggested, grossly, tuberculous osteomyelitis, and this diagnosis was later confirmed by the microscopic sections.

The tuberculous nature of the lesion having been demonstrated at the postmortem examination, many more sections were cut from the old operative specimens, and in some of these sections areas were found which were realized to be tubercles. The making of a correct diagnosis pathologically prior to autopsy would have been most difficult, owing to the sparse and atypical areas of tuberculous structure.

The question may pertinently be raised as to whether or not this was a superimposed tuberculous infection resulting from a general dissemination. Clinically, there was no evidence of a dissemination of this sort until a few weeks after the last operation, for until that time the patient's general condition had been satisfactory. The pathologic evidence against such a dissemination is more conclusive since minute miliary tubercles were not found and since the character of the tubercles found in the femur was different from that of the tubercles found elsewhere. Those in the sections from the femur were old in appearance, with epithelioid and giant cells, whereas the sections from the lung and brain showed considerable caseation and few giant cells. While we do not consider the tuberculosis of the femur to be a primary focus,

---

1. Lovett, R. W., and Wolbach, S. B.: Roentgenographic Appearance, Diagnosis and Pathology of Some Obscure Cases of Bone Lesions, *Surg., Gynec. & Obst.* **31**:111, 1920.

2. Bromer, R. S., and Downs, E. E.: Tuberculosis of the Diaphysis, *Am. J. Roentgenol.* **24**:617 (May) 1933.

because the old hilus glands and thickened pleura seem to antedate this, so far as the patient's acute illness was concerned, we believe that the differentiation in the character of the tubercles designates the osteomyelitis as the initial lesion.

In classifying this case, Caan's<sup>3</sup> modification of Küttner's<sup>4</sup> classification, that of tuberculosis of the shaft of the central type, in which the caseating lesion has been modified by a marked periosteal reaction, seems to be most descriptive. It also closely resembles the description given by Schinz,<sup>5</sup> that of an osteosclerotic type of tuberculosis of the bone affecting the shaft of a long bone but not involving the joints, with an appearance of the cortex undifferentiated from the periosteal



Fig. 7.—High power photomicrograph of a specimen from the last operation (Oct. 5, 1932). The section shows the granulation tissue with formation of tubercles.

stratification spread out in multiple foci over the shaft. This was particularly noteworthy and most descriptive of the appearance of the femur at the last operative procedure in this case (fig. 9).

We should like to emphasize the extreme difficulty in the differential diagnosis of tuberculosis of the shaft of a long bone, as exemplified

3. Caan, Paul: Die Schafttuberkulose der langen Röhrenknochen, *Beitr. z. klin. Chir.* **128**:691, 1923.

4. Küttner, H.: Die Osteomyelitis tuberkulosa der Schäfte langer Röhrenknochen, *Beitr. z. klin. Chir.* **24**:449, 1899.

5. Schinz, H. R.: *Lehrbuch der Roentgendiagnostik*, Leipzig, Georg Thieme, 1928; quoted by Bromer and Downs.

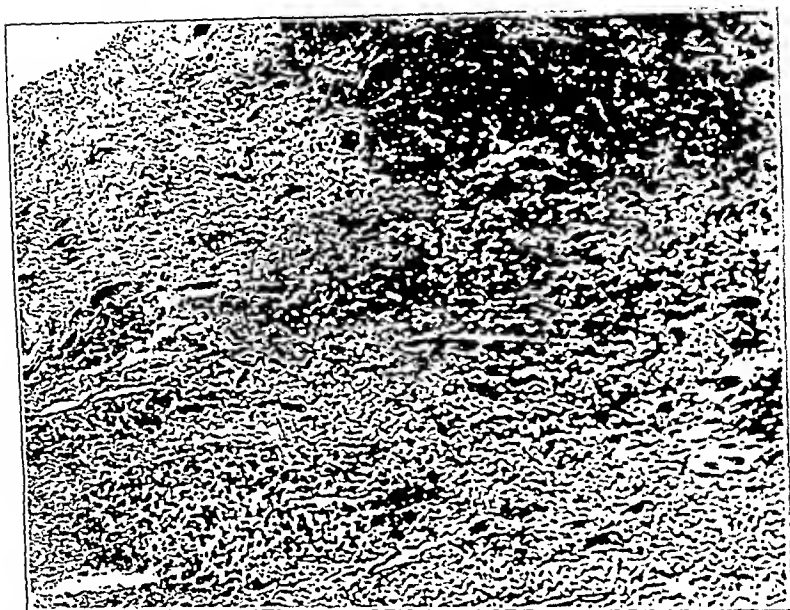


Fig. 8.—Photomicrograph of a specimen from the second operation (Aug. 8, 1932). The section shows a collection of mononuclear and epithelioid cells, which in retrospect suggest tuberculous granulation tissue.



Fig. 9.—Photomicrograph of a section of the femur from the last operation, showing new bone with sclerosis.



by this report. This difficulty and the infrequent occurrence of the condition lead one to consider tuberculosis as a possible cause of every obscure diaphyseal lesion.

#### SUMMARY

A case is presented in which there was an obscure and fulminating destructive lesion of the shaft of the left femur and in which operations and general supportive measures seemed to have only a slight effect, the last surgical procedure being followed by a rapid decline and death. Postmortem examination revealed previously unsuspected tuberculosis of the left femur and also tuberculous lesions in the brain, the lungs and other viscera. Further pathologic examination of the old operative specimens in the light of these observations demonstrated the existence of primary tuberculosis of the shaft of the femur.

# HISTOLOGIC EFFECTS OF INTRAVENOUS SCLEROSING SOLUTIONS ON SUBCUTANEOUS TISSUES

HOWARD R. MAHORNER, M.D.

AND

ALTON OCHSNER, M.D.

NEW ORLEANS

Injection into varicose veins of the lower extremities has become the most popular and is undoubtedly the best method of treatment in most cases. In a previous paper by Garside and one of us (Ochsner)<sup>1</sup> and in a previous paper by us<sup>2</sup> the results of histologic studies of the effects of intravenous injection of twenty-nine sclerosing solutions are reported in detail. In each of those papers attention was called to the fact that the endothelium was partially or completely destroyed by an effective thrombosis-producing agent, and mention was made of the fact that such destruction was essential for the precipitation of a thrombus. In our last paper<sup>2</sup> we also showed that the effect of some sclerosing agents was not only the destruction of the intima but also at times the production of coagulation necrosis of the media. The intima, when sufficiently injured, disappeared so that it was not possible to observe the results of the action of the sclerosing solution on the cells. Because of the destructive effect of sclerosing agents on the endothelium of the veins and as an accidental perivenous injection of the sclerosing substance occasionally occurs clinically, it was considered expedient to investigate the effect of sclerosing solutions on extravascular cells.

## METHOD

Dogs were used as the test animals. At four separate points on each side of the ventral thoracic and abdominal wall 2 cc. each of eight of the sclerosing solutions to be tested was injected subcutaneously. Thus each dog was given eight injections, each of a different solution. The areas into which the injection was made was carefully marked with black paint, and subsequently each area was observed and repainted if necessary. Five dogs were given injections of each solution. The solutions used were: sodium salicylate, 40 per cent; invert sugar, 75 per cent; quinine and ethyl carbamate (urethane); equal parts of dextrose, 50 per cent, and sodium chloride, 30 per cent; sodium morrhuate (Searle), 5 per cent; sodium gynocardate, 3 per cent; sodium gynocardate, 5 per cent, and sodium hydriocarpate, 5 per cent. The animals were killed at one hour, twelve hours, twenty-four hours, four days and ten days following injection. Thus a piece of skin together with subcutaneous tissue was obtained for each of the sclerosing

---

From the Department of Surgery, Tulane University School of Medicine.

1. Ochsner, A., and Garside, Earl: *The Intravenous Injections of Sclerosing Substances: Experimental Comparative Study of Changes in the Vessels*, Ann. Surg. **96**:691, 1932.

2. Ochsner, A., and Mahorner, H. R.: *Studies of the Comparative Value of Intravenous Sclerosing Substances*, Proc. Soc. Exper. Biol. & Med. **30**:1180, 1933.

solutions for each period of time. In addition, in two extra dogs 2 cc. of turpentine was injected at five points, and the areas into which the injections were made were removed subsequently at intervals of time corresponding to those at which the other animals were killed.

Sections from the blocks of skin and subcutaneous tissue were stained for microscopic study with hematoxylin and eosin and Van Gieson's connective tissue stain.<sup>2a</sup>

In studying the sections the different changes were graded 0, 1, 2, 3 and 4, 1 designating a slight change and 4 indicating a complete change in the area involved. On each section observation was made and recorded in grades for each of the following changes: hyperemia, edema, leukocytic infiltration (neutrophils), pyknosis, karyorrhexis, karyolysis, coagulation necrosis, connective tissue proliferation, fibrosis, thrombosis, injury to the cutis vera (ulceration), hemorrhage, disappearance of fat, lymphocytic infiltration, liquefaction necrosis and the presence of wandering cells.

The type, though not the grade, of the reactions induced by each of the sclerosing solutions was similar. The varying grades of reaction are shown in the table. The type of reaction, graphically illustrated in figure 1, is as follows:

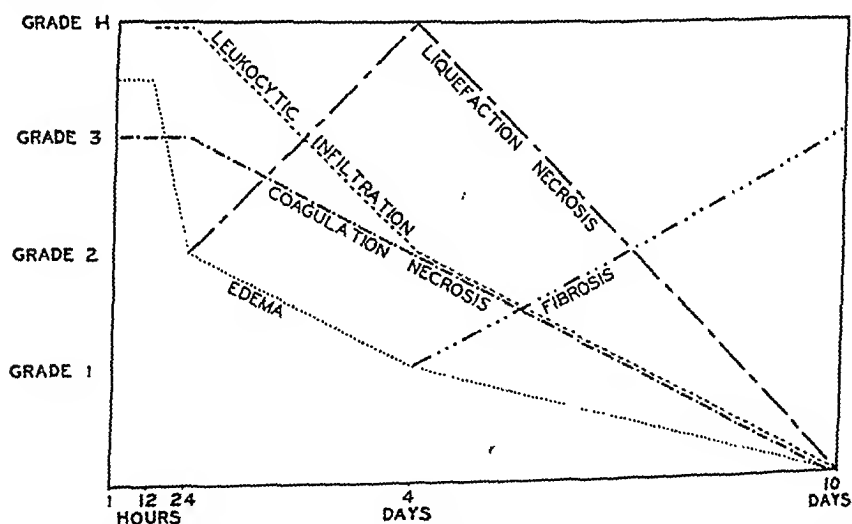


Fig. 1.—Graphic representation of the type of histologic changes occurring in tissue after subcutaneous injection of sclerosing solutions. The ordinate represents the grade of reaction, grade 4 being marked and grade 1 slight. The abscissa represents the time up to ten days at which the tissue was removed. Edema was present one hour after injection, but leukocytic infiltration was noticed only after twelve hours and gradually subsided after twenty-four hours. Coagulation necrosis was noticed in tissues removed after one hour and was gradually replaced by liquefaction necrosis. Fibrosis was most marked after ten days.

2a. Stain deeply in Delafield's alum hematoxylin; wash; stain in 5 cc. of 1 per cent aqueous solution of acid fuchsin and 100 cc. of saturated aqueous solution of trinitrophenol. Dehydrate in alcohol. Clear in xylene and mount.

*Grades of Reactions Produced by Sclerosing Substances After Different Periods of Time*

	Hyper- emia	Edema	Leuko- cytic Infl- tration	Pyknosis	Karyo- rhexis	Karyo- lysis	Con- gulation Necrosis	Connective Tissue Prolif- eration	Throm- bosis	Injury to Cutis Vern	Hemor- rhage	Disappear- ance of Fat	Lympho- cytic Infl- tration	Lique- faction Necrosis	Wander- ing Cells
<b>Sodium sulfocyanate, 40%</b>															
1 hour.....	4	1	1	1	2	3	3	0	0	0	0	0	0	0	0
12 hours.....	3	3	2	1	0	1	2	0	0	0	0	0	0	0	0
24 hours.....	3	3	2	2	3	2	2	0	0	3	0	2	2	2	0
4 days.....	2	1	1	0	3	2	2	1	0	0	2	2	2	1	0
10 days.....	2	0	2	0	0	2	2	2	0	0	0	2	2	0	0
<b>Invert sugar, 75%</b>															
1 hour.....	1	0	0	0	0	1	1	0	3	0	0	0	0	0	0
12 hours.....	2	2	2	0	0	1	1	0	0	0	1	2	0	0	0
24 hours.....	2	2	2	0	1	1	0	0	0	0	2	0	0	0	0
4 days.....	2	2	1	0	0	0	0	1	0	0	0	0	1	0	0
10 days.....	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0
<b>Sodium glycinate, 5%</b>															
1 hour.....	3	0	0	0	0	3	4	0	0	0	0	2	0	0	0
12 hours.....	3	3	4	0	0	3	4	0	3	0	0	2	0	2	0
24 hours.....	3	2	2	0	0	3	1	2	1	0	0	2	2	3	0
4 days.....	1	1	2	0	2	1	1	3	0	0	0	2	0	2	0
10 days.....	2	1	2	0	2	1	1	3	0	0	0	2	0	2	0
<b>Quinine and ethyl carbonate</b>															
1 hour.....	2	3	0	0	2	2	2	0	0	0	1	1	0	0	0
12 hours.....	3	3	2	0	0	0	1	0	0	0	0	0	0	0	0
24 hours.....	2	2	2	0	0	0	2	0	0	0	2	0	0	0	0
4 days.....	3	2	2	0	0	0	3	2	0	0	2	1	0	0	0
10 days.....	0	1	0	0	0	0	0	2	0	0	0	1	1	0	0
<b>Searle's sodium morphinate, 5%</b>															
1 hour.....	3	0	0	0	0	3	3	0	0	0	0	1	0	1	0
12 hours.....	4	3	4	0	0	3	3	0	0	0	0	2	0	2	0
24 hours.....	3	3	4	0	0	3	3	0	0	0	2	2	0	2	0
4 days.....	2	2	2	0	0	2	2	2	0	0	1	2	2	2	0
10 days.....	1	0	0	0	0	0	0	2	0	0	0	2	0	0	0
<b>Sodium glycinate, 3%</b>															
1 hour.....	3	0	0	0	1	3	1	0	0	0	0	0	0	0	0
12 hours.....	3	2	3	0	0	3	4	0	0	0	0	2	0	0	0
24 hours.....	3	2	3	0	0	3	4	0	0	0	2	2	0	0	0
4 days.....	2	2	2	0	0	2	2	3	0	0	1	2	0	2	0
10 days.....	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0
<b>Dextrose, 50%, and sodium chloride, 30%, equal parts</b>															
1 hour.....	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
12 hours.....	3	3	2	0	0	0	0	0	0	0	0	0	0	0	0
24 hours.....	3	2	2	0	0	0	0	0	0	0	2	1	0	0	0
4 days.....	2	1	1	0	0	0	1	0	0	0	2	1	0	0	0
10 days.....	3	2	1	1	1	3	1	3	0	1	2	2	0	0	0
<b>Sodium hydnocarpate, 5%</b>															
1 hour.....	3	0	0	0	0	2	2	0	0	0	1	0	0	0	0
12 hours.....	3	3	3	0	0	3	3	0	0	0	0	1	0	2	0
24 hours.....	2	2	2	0	0	2	2	3	0	0	0	1	2	1	0
4 days.....	2	2	3	0	0	0	0	3	0	0	0	2	2	2	0
10 days.....	0	0	0	0	0	0	0	0	3	0	0	2	2	2	0

\* Ulcer.

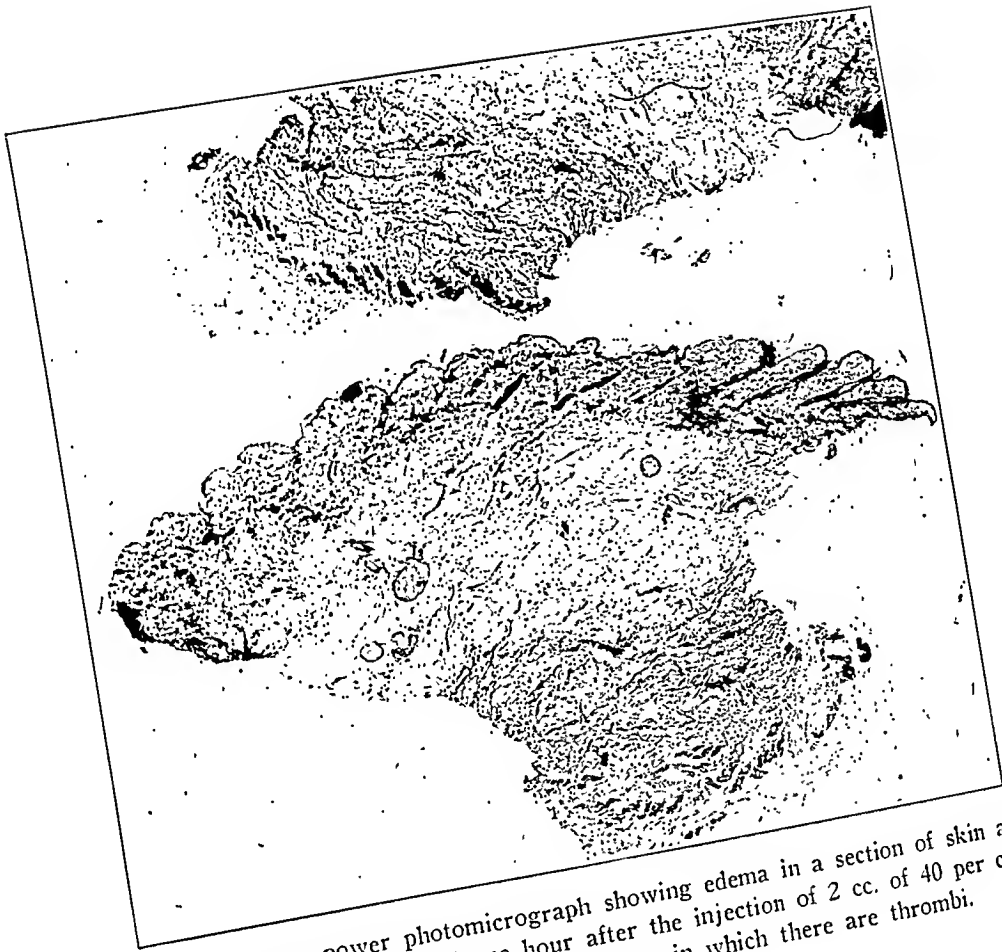


Fig. 2.—Low power photomicrograph showing edema in a section of skin and subcutaneous tissue, removed one hour after the injection of 2 cc. of 40 per cent sodium salicylate. Several vessels are shown in which there are thrombi.

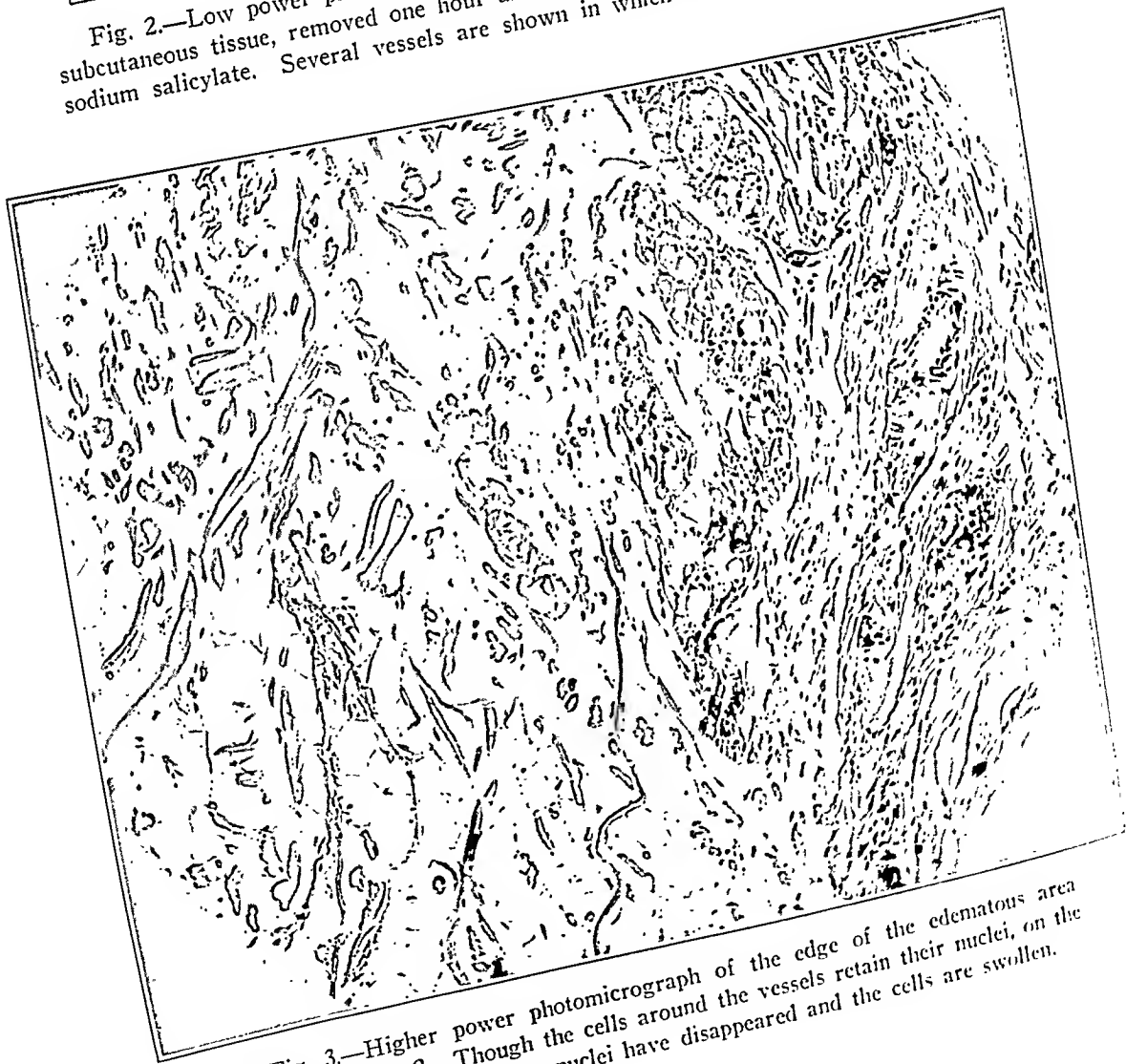


Fig. 3.—Higher power photomicrograph of the edge of the edematous area shown in figure 2. Though the cells around the vessels retain their nuclei, on the opposite side of the field the nuclei have disappeared and the cells are swollen.

*One Hour.*—After one hour the tissues in the area into which injection was made were markedly edematous, and the vessels showed a moderate amount of hyperemia (fig. 2). Besides these changes, there was disappearance of the nuclei (karyolysis; coagulation necrosis {figs. 2 and 3}). The remaining outlines of the cells were swollen. This necrosis of cells was found to be complete (grade 4) after the injection of 5 per cent sodium gynocardate, and marked (grade 3) after the injection of 5 per cent sodium morrhuate (Searle), 40 per cent sodium salicylate and 3 per cent sodium gynocardate. It was graded only 2 in tissues into which quinine and ethyl carbamate and 5 per cent sodium hydriocarpate were injected, and there was no disappearance of nuclei in sections into which equal parts of 50 per cent dextrose and 30 per cent sodium chloride had been injected. There was no cellular exudate in any of the sections.

*Twelve Hours.*—The most obvious difference between the sections obtained one hour after injection and those obtained twelve hours afterward was the presence of cellular exudate in the latter. This was manifested in the section by a solid wall of leukocytes about 1 mm. in width that surrounded the necrotic area on either side (figs. 4 and 5). This resembled a small sterile abscess with necrosis of the tissue in the center surrounded by a zone of neutrophilic leukocytes and in turn circumvented by an area of hyperemia and edema. At this stage the edema had subsided somewhat, but liquefaction necrosis was not evident.

*Twenty-Four Hours.*—After twenty-four hours beginning liquefaction of the necrotic area was observed. Disappearance of fat was obvious. The surrounding zone of leukocytes was still manifest and in most of the sections was identical with that in the sections obtained twelve hours after injection. In some instances beginning proliferation of fibroblasts was observed in the area surrounding the zone of leukocytes. Edema and hyperemia were less marked. The processes of repair were beginning.

*Four Days.*—After four days hyperemia and edema were only slight. The leukocytes had not entirely disappeared, but there was an appreciable diminution in their numbers. The necrotic central zone had become liquefied, and in it were observed only cellular detritus and a few leukocytes (figs. 6 and 7). Proliferation of connective tissue around this zone was more marked, and the new connective tissue cells were more mature. A few large wandering cells were observed in some of the sections. It was evident that nature was repairing the injury by a connective tissue scar.

*Ten Days.*—The typical change observed after ten days consisted of fibrosis at the site of injection together with absence of fat (fig. 8). The exudative stage of inflammation (leukocytes, edema and hyperemia) had usually disappeared, and a scar, the stage of repair, was all

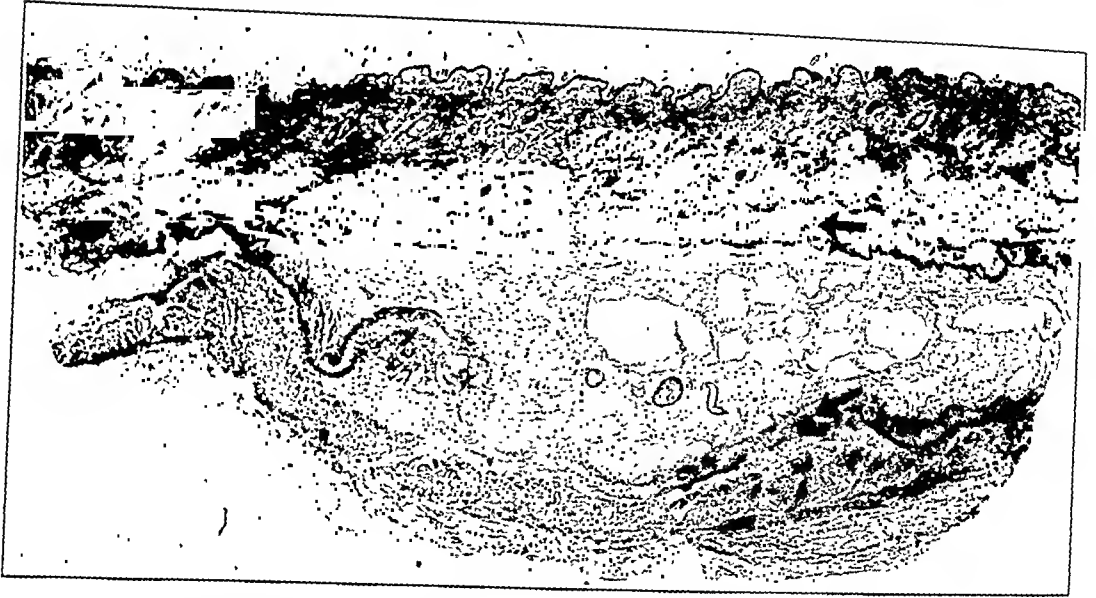


Fig. 4.—Photomicrograph of tissue removed twelve hours after the subcutaneous injection of 5 per cent sodium gynocardate, showing a central necrotic area surrounded by a zone of leukocytes (marked with arrows). Thrombi are present in the vessels in the necrotic area.

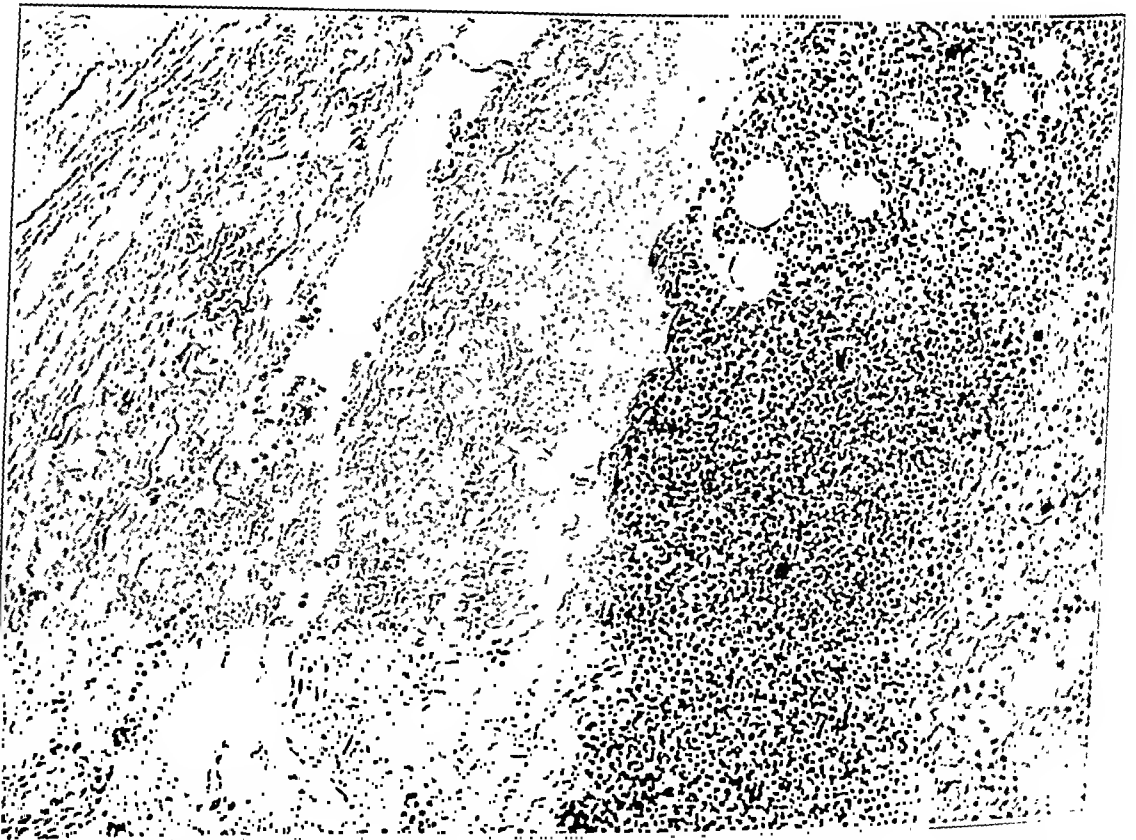


Fig. 5.—Higher power photomicrograph of the edge of the zone of leukocytes indicated in figure 4 by arrows. The necrotic area, in which there is an occasional leukocyte, is shown bordered by the zone of leukocytic infiltration.

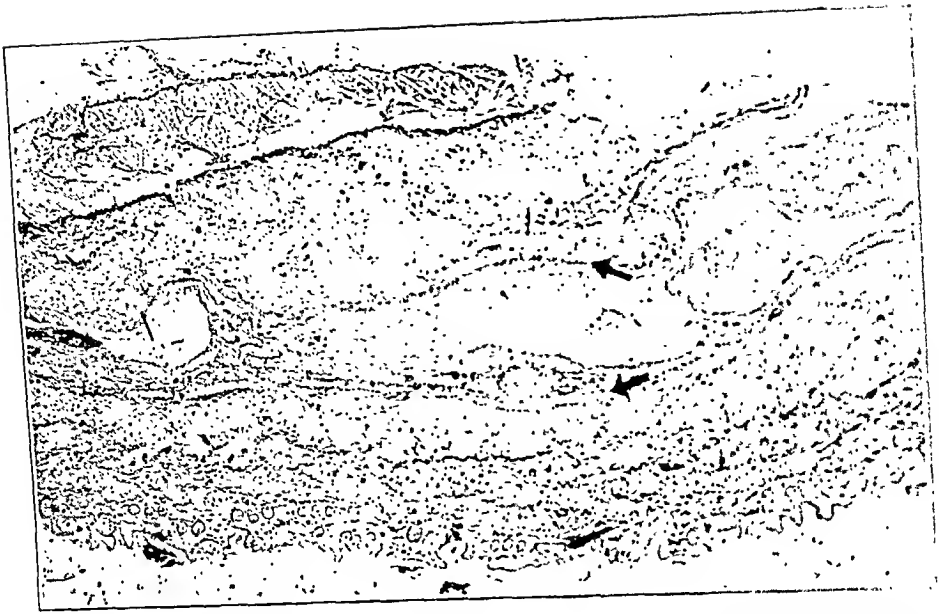


Fig. 6.—Photomicrograph of subcutaneous tissue four days after the injection of 3 per cent sodium gynocardate. The central area has undergone liquefaction and is surrounded by a fibrous wall (indicated by arrows).



Fig. 7.—Higher power photomicrograph of the edge of the fibrous wall and central area shown in figure 6. Cellular detritus and a few neutrophils are shown, bordered by the fibrosed area.



there was to be found. In a few of the sections slight evidence of exudative reaction remained.

*Other Changes.*—Hemorrhage: Hemorrhage was observed in but twelve of the sections. It was never marked and may have been due to injury of a vessel at the time of injection.

*Lymphocytic Infiltration:* Lymphocytes were noted in small numbers in four of the sections obtained four days after injection, in three of those obtained after ten days, and in one (5 per cent sodium hydno-carpate) of the sections examined after twenty-four hours.



Fig. 8.—Photomicrograph of subcutaneous tissue removed ten days after the injection of 5 per cent sodium morrhuate (Searle). An area of dense fibrosis is seen.

*Thrombosis:* Thrombosis was found in the small veins and arteries of a necrotic area after injection of 40 per cent sodium salicylate, 5 per cent sodium gynocardate, 5 per cent sodium hydno-carpate and quinine and ethyl carbamate. It was the result of injury (necrosis) to the wall of the vessel. That it was not observed after injection of the other substances is no indication that it does not occur. Conversely, the occurrence of thrombosis is no indication of the thrombus-producing efficiency of the solutions, because vessels of an appreciable size may not have been present in the injured area observed or solutions may not have come in contact with the wall of a particular vessel in sufficient concentration to produce necrosis. Thrombosis as well as fibrosis after extravascular injection of sclerosing solutions into the tissues is of prac-

tical importance in the treatment of hemorrhoids by injection when the case falls in the category of the carefully selected few suitable for that type of treatment.

Injury to the Cutis Vera: Ulceration was observed only twice after injection of the sclerosing solutions, viz., in the section obtained twenty-four hours after the injection of 40 per cent sodium salicylate, and in that obtained ten days after the injection of equal parts of 5 per cent dextrose and 30 per cent sodium chloride. These two instances we do not regard as evidence that the 40 per cent solution of sodium salicylate and the solution of equal parts of 50 per cent dextrose and 30 per cent sodium chloride are more likely than other solutions to produce ulceration after a technical error in injection. As a matter of fact, these solutions, especially the latter, produced less necrosis of tissues than did the others. The ulceration in these instances probably resulted from the fact that the solutions were injected closer to or partially into the cutis vera.

*Effect of Injection of Turpentine.*—As subcutaneous injections of turpentine have been made to produce a sterile abscess, the effect produced by the injection of turpentine was compared with that produced by sclerosing agents. Two cubic centimeters of turpentine injected subcutaneously produced more extensive and more complete destruction (necrosis) of tissue than did the eight sclerosing solutions. Moreover, the inflammatory reaction was more marked and evidently more prolonged. Of three areas permitted to remain four days or longer after the injection of 2 cc. of turpentine subcutaneously, all showed ulceration. The fibrosis resulting in the deeper tissues was more marked than that noted after the injection of the sclerosing solutions. Turpentine injected subcutaneously produces a sterile abscess with marked inflammatory reaction and ulceration of the skin.

#### COMMENT

In the intravenous injection of sclerosing solutions it is necessary for the endothelium to be destroyed for the precipitation of a thrombus.<sup>2</sup> So the solution used should have the property of injuring cells by direct action. That the commonly used solutions do have this property has been definitely shown in this study. Necrosis of the cell is produced. The amount of material used clinically for injection has no systemic reaction but is sufficient to injure the endothelium locally. Clinically, it is obviously of value to occlude by pressure the vein above and below the area into which the injection is to be made and to maintain this occlusion for a few minutes in order to allow time for action of the solution on the intima in that vicinity. Complete circumferential destruc-

tion of the intima and adherence of the clot to the wall of the vein insure less chance of recurrence of varicosity.

Perivenous injection of sclerosing solutions produces thrombosis and scarring and from the experimental evidence described is a rational method for the treatment of hemorrhoidal varicosities by injection in that relatively small group of cases clinically suitable for this type of treatment.

Whereas it is difficult from our study to state definitely any indications as to the relative efficiency of the sclerosing solutions studied, we observed that 5 and 3 per cent sodium gynocardate, 5 per cent sodium morrhuate (Searle) and 40 per cent sodium salicylate produced a more severe degree of necrosis than quinine and ethyl carbamate, and 5 per cent sodium hydncarpate, which in turn produced more complete necrosis than 75 per cent invert sugar and equal parts of 50 per cent dextrose and 30 per cent sodium chloride. Though no definite conclusions can be drawn from this, when comparing this fact with the results of our former study on the thrombus-producing efficiency of sclerosing solutions<sup>2</sup> we find that there is a similar gradation of effectiveness.

#### SUMMARY

Two cubic centimeters of the following sclerosing solutions was injected subcutaneously at different points into dogs: sodium morrhuate (Searle), 5 per cent; sodium gynocardate, 5 and 3 per cent; sodium hydncarpate, 5 per cent; quinine and ethyl carbamate; sodium salicylate, 40 per cent; invert sugar, 75 per cent, and equal parts of dextrose, 50 per cent, and sodium chloride, 30 per cent. The areas into which the injections were made were removed after one hour, twelve hours, twenty-four hours, four days and ten days.

We found that the solutions produced necrosis of the subcutaneous tissue with a zone of inflammatory reaction surrounding it, liquefaction necrosis and subsequently fibrosis—in other words, a sterile abscess, which resulted in ulceration only twice. Since destruction of endothelium is essential in the intravenous injection of sclerosing solutions for the treatment of varicose veins, the property of injuring cells locally is desirable provided the systemic effect is not untoward. Five and 3 per cent sodium gynocardate, 5 per cent sodium morrhuate (Searle) and 40 per cent sodium salicylate seem to produce more complete necrosis of tissues than do the other solutions tested by us. This is in similar ratio to their thrombus-producing effectiveness as tested by us by intravenous injection. Forty per cent sodium salicylate is not advocated for clinical use.<sup>1</sup>

## CONCLUSIONS

Subcutaneous injection of commonly used sclerosing solutions produces necrosis and an inflammatory reaction, a sterile abscess with subsequent repair by fibrosis. Rarely does it lead to ulceration of the skin.

Five and 3 per cent sodium gynocardate, 5 per cent sodium morrhuate (Searle) and 40 per cent sodium salicylate produce more pronounced injury to cells locally than quinine and ethyl carbamate and 5 per cent sodium hydno carpate, and the latter two in turn produce more severe injury than 70 per cent invert sugar and equal parts of 50 per cent dextrose and 30 per cent sodium chloride. This relation is similar to their relative effectiveness as thrombus producers as formerly shown by us experimentally by intravenous injection.

# CARCINOMA OF THE BODY AND TAIL OF THE PANCREAS

HENRY K. RANSOM, M.D.

ANN ARBOR, MICH.

The usual conception of the clinical syndrome evoked by carcinoma of the pancreas and the accounts of this condition ordinarily given in the textbooks of medicine and surgery picture it as essentially one of intense progressive obstructive jaundice with rapid and extreme emaciation. The malady is most often painless, although occasionally there may be epigastric pain, which is apt to be of the paroxysmal type. When in addition to the aforementioned clinical findings, discovered in a patient during middle age or late in life, a distended gallbladder can be palpated, then, in accordance with the well known law formulated by Courvoisier, the existence of carcinoma of the head of the pancreas is almost certain.

In spite of the fact that this disease is not infrequently met with in the large teaching hospitals of the country, various statistical studies showing that it comprises between 1 and 2 per cent of all cases of cancer, comparatively few papers dealing with the subject have appeared during the past few years. From the time of the first description of this lesion by Mondière<sup>1</sup> in 1836, the subject seems to have appealed especially to French investigators, and important contributions have been made by Ancelot,<sup>2</sup> Bard and Pic,<sup>3</sup> Mirallie<sup>4</sup> and Parmentier and Chabral.<sup>5</sup> Perhaps the gloomy prognosis which must necessarily be given to patients afflicted with this disease in spite of any form of surgical therapy hitherto employed is a factor in this apparent disinterestedness on the part of physicians and surgeons, although the employment of cholecystenterostomy for the amelioration of symptoms, particularly the distressing pruritus so often the accompaniment of chronic jaundice, has now become a well recognized palliative procedure.

---

From the Department of Surgery, University of Michigan.

Presented before the Detroit Academy of Surgery, March 8, 1934.

1. Mondière, quoted by Parmentier and Chabral.<sup>5</sup>

2. Ancelot, E.: *Maladies du pancréas*, Paris, F. Savy, 1864, p. 53.

3. Bard, L., and Pic, Andrien: *Cancer primitif du pancréas*, *Rev. de méd.* Paris 8:257 (April) 1888.

4. Mirallie, C.: *Cancer primitif du pancréas*, *Gaz. d. hôp.* 46:889 (Aug. 19) 1893.

5. Parmentier, E., and Chabral, E.: *Les tumeurs solides du pancréas*, in Roger, G. H.; Widal, F., and Teissier, P. J.: *Nouveau traité de médecine*, Paris, Masson & Cie, 1923, vol. 15, p. 197.

In a critical study of large groups of cases, many of them coming to autopsy, it becomes evident that carcinoma of the pancreas is not invariably confined to the head of the organ, in which position it is of course admirably situated for compression of the distal portion of the ductus communis choledochus as the latter passes through or behind the gland. In a fair proportion of cases of pancreatic cancer, the lesion has been found situated in the body of the gland or, more rarely, in the tail of the organ, in which instances it may attain considerable size and even metastasize extensively before jaundice is produced. Table 1 indicates the relative incidence of cancer in the head, body and tail of the pancreas in several of the larger series that have been reported and shows that carcinoma arising in portions of the pancreas other than the head is not of great rarity.

It should be pointed out that entirely different syndromes are provoked by pancreatic cancer, depending on the portion of the gland primarily involved. Thus, while progressive painless jaundice is the rule

TABLE 1.\*—Location of the Lesion in Cases of Carcinoma of the Pancreas

Author	General	Head	Body	Tail
.....	11	11	2	2
.....	10	39	3	3
.....	1	20	5	5
.....	15	25	5	5
.....	4	24	5	5
.....	65	33	5	5
.....	21	10	13	..

\* Adapted from Klefer.

in cancer of the head, the symptom of pain unaccompanied by jaundice dominates the picture in carcinoma of the body, whereas the rare cancers of the tail are often characterized by relatively few symptoms and produce a rather vague and ill defined clinical picture.

Concerning carcinoma in these more unusual situations, Chauffard<sup>6</sup> in 1908 first called attention to carcinoma of the corpus as a distinct clinical entity. In the discussion of his three similar cases in which the diagnosis was verified by laparotomy in two and by necropsy in one he laid particular stress on the great severity and the type of pain from which these patients suffered, the rapid and severe emaciation and the complete absence of jaundice. According to Chauffard's observations, the initial symptom in his cases was epigastric pain occurring in a patient who had previously been in good health; it was sudden in its onset, beginning on the left but soon becoming more or less generalized over the abdomen and radiating to the back, the chest or scapulae. It was unrelated to the ingestion of food. This paroxysmal pain, because of

6. Chauffard: Le cancer du corps du pancréas, Bull. Acad. de méd., Paris 22:913, 1908.

its great severity, seemed to him comparable only to the most intense tabetic crises. Nausea and vomiting were not symptoms of great importance.

As from time to time carcinoma of the body or tail of the pancreas has been unexpectedly encountered at operation in cases in which carcinoma of the colon or stomach had most often been suspected beforehand, it seemed desirable to assemble the records of these cases for careful analysis, in order to learn, if possible, more of the signs and symptoms by which the condition may be recognized clinically, as well as to follow the life history of the disease. From July 1, 1925, to Jan. 1, 1934, sixteen cases of carcinoma of the body or tail of the pancreas were observed in the University Hospital. In every case the diagnosis was verified by operation or necropsy. The operative diagnosis was in practically all instances made by one of the senior surgeons of the hospital, the majority of the operations having been performed by Dr. Hugh Cabot or Dr. Frederick A. Collier. Microscopic confirmation of the diagnosis was not feasible in all of the cases in which operation was performed, although whenever possible biopsy specimens were taken. The hospital records show that during this same period fifty-eight cases of carcinoma of the head of the pancreas were seen in the medical and surgical departments. The diagnosis was confirmed by surgical operation or necropsy in thirty-nine of these fifty-eight cases and based on sound clinical evidence in the remaining nineteen (Collier and Winfield<sup>7</sup>).

#### AGE AND SEX INCIDENCE

Table 2 shows the age and sex incidence. The occurrence of approximately twice as many men as women in the series is a finding in accord with the observations of other writers, viz., Mirallie, Da Costa,<sup>8</sup> Speed<sup>9</sup>

TABLE 2.—Incidence According to Age and Sex in the Cases Reported

Age	Cases	Sex	Cases
40-49 years.....	3	Males.....	11
50-59 years.....	5	Females.....	5
60-69 years.....	8		<hr/> 16
	<hr/> 16		

The youngest patient was 40 years old, and the oldest patient, 69 years; the average age was 57 years

7. Collier, F. A., and Winfield, J. M., Jr.: Evaluation of Palliative Operations for Cancer of the Pancreas, *Am. J. Surg.* **25**:64 (July) 1934.

8. Da Costa, J. M.: Cancer of the Pancreas, *North America M. Chir. Rev.* **2**:883, 1858; *Tr. Path. Soc. Philadelphia* **1**:8 and 709, 1860.

9. Speed, Kellogg: Carcinoma of the Pancreas, *Am. J. M. Sc.* **160**:1 (July) 1920.

and Fletcher,<sup>10</sup> in their studies of carcinoma of the pancreas in its broader aspects. From this table it will also be noted that all of the patients were aged or in late middle life, there having been no instances of pancreatic cancer in the very young, and we have not observed increasing numbers of cases in the earlier years of life, as has been our recent experience with cancer of the stomach, rectum and colon.

#### SYMPTOMS

*Pain.*—By far the most outstanding symptom of carcinoma of the body of the pancreas is abdominal pain, which is usually of extreme severity and most often intermittent in character, with a residual soreness between the actual paroxysms of pain. In thirteen of the sixteen cases, pain was the chief complaint for which the patient sought relief, and it was a major symptom in all the cases (table 3). In fourteen cases it was the first symptom to be noticed by the patient, while in the remaining two cases it was preceded by vague symptoms of con-

TABLE 3.—*Chief Complaint in the Cases Reported*

	Cases
Abdominal pain .....	13
Mass in the epigastrium .....	1
Epigastric distress .....	1
Loss of appetite, weakness .....	1
	<hr/> 16

stipation and malaise for two or three months, symptoms which caused the patient little concern before the advent of pain. Having once appeared, the abdominal pain tended to progress rapidly and was soon accompanied by marked general deterioration and exhaustion.

Since pain constituted such a severe and important symptom, an attempt has been made to analyze it in detail. The pain of pancreatic carcinoma in general is described by Kiefer<sup>11</sup> as being of three types: (1) a dull, steady, severe ache in the midepigastrium, sometimes radiating to the lower part of the back; (2) pain occurring in paroxysms beginning near the umbilicus and radiating to the back and chest, and (3) colicky pain in the right upper quadrant resembling gallstone colic. Table 4 indicates the location of the pain at the time of its onset in the group of cases under consideration. In this small series it is obviously impossible to conclude that there is any one region in which the pain is characteristically found. The midepigastria region was men-

10. Fletcher, T. B.: Cancer of the Pancreas, *Tr. A. Am. Physicians* **34**:284, 1919.

11. Kiefer, E. D.: Carcinoma of the Pancreas, *Arch. Int. Med.* **40**:1 (July) 1927.



tioned most frequently, but since such a wide variety of other lesions are liable to produce epigastric pain, little assistance in diagnosis is obtained from this fact. From the point of its original beginning, the pain usually tended to become more generalized throughout the abdomen as the disease advanced. In table 5 the incidence and forms of radiation of pain are shown. Radiation was definitely described in about one half of the cases, and when it occurred it was most often toward the back or the chest, although no entirely constant form was noted.

The qualitative type of the pain is also of interest. In table 6 a classification of pain according to general type is made. As will be noted, the pain persisted throughout the course of the illness as a dull, steady ache in eight cases, whereas in the remaining eight cases

TABLE 4.—*Location of Pain at the Time of Onset in the Cases Reported*

	Cases
Lower part of abdomen (generalized).....	2
Midepigastrium .....	7
Back .....	1
Right hypochondrium .....	3
Left hypochondrium .....	1
Right iliac region.....	1
Both iliac regions.....	1
	<hr/> 16

TABLE 5.—*Radiation of Abdominal Pain in the Cases Reported*

	Cases
No radiation .....	9
To back .....	4
To back and the right hip and thigh.....	2
To back and the right side of chest.....	1
	<hr/> 16

the patient complained of paroxysmal or colicky pain. In regard to the steady, dull aching midepigastrium pain mentioned earlier, the descriptions given by the French writers seem especially appropriate. Mirallie spoke of the pain as being boring or tearing, while another writer called it a destroying pain. Malus<sup>12</sup> described the paroxysmal pains as "atrocious." Some observers ascribe these paroxysms of pain to an obstruction of the pancreatic duct which interferes with the discharge of the pancreatic secretion; hence they regard the pain as true pancreatic colic. On account of the absence of obstructive jaundice in the cases under discussion the factor of obstruction of the biliary tract, suggested by some, may be excluded. Perhaps the most interesting

12. Malus: *Etude statistique et clinique du cancer primitif du corps du pancréas*, *Gaz. méd. de Nantes* 28:530, 1910.

and certainly one of the most plausible explanations of the excruciating, shooting pains is the one originally suggested by Chauffard and based on the intimate relation between the body of the pancreas and the solar plexus. The lower half of this plexus is closely associated with the posterior surface of the body of the gland, and numerous nerve filaments leaving the plexus perforate the substance of the pancreas.

In table 7 are listed the factors which seemed to be responsible in some degree for the aggravation or relief of the pain. Here again the factors are so varied that no definite conclusions can be drawn. It should be mentioned that in general the attacks of pain occurred without provocation of any sort, and likewise cessation of the attack seemed to be unrelated to extrinsic factors. In this series of cases changes of

TABLE 6.—*Type of Pain in the Cases Reported*

	Cases
Dull (aching, steady) .....	8
Colicky (throbbing, shooting) .....	5
Dull becoming colicky .....	1
Colicky becoming constant.....	2
	<hr/> 16

TABLE 7.—*Alteration of Pain in the Cases Reported*

	Cases
Relief with bowel movement .....	4
Relief with soda .....	6
Pain aggravated by food.....	4
Relief with vomiting .....	1
No changes noted.....	5
	<hr/> 20

body position, such as lying down, standing or sitting, seemed ineffectual in affording relief. While the ingestion of food was not a factor in initiating the attack of pain during a paroxysm it seemed to accentuate the severity, until most of the patients refused food during the height of an attack.

*Nausea and Vomiting.*—Table 8 indicates that nausea and vomiting were not prominent symptoms and if present were not of great severity, being an accompaniment of the paroxysms of pain rather than important independent symptoms.

*Anorexia.*—A curious finding was the fact that, in spite of unmistakable evidence of cachexia, loss of appetite was present in only three cases, the patients in the other cases having no aversion to food during the entire course of the disease, with the exception of the intolerance for food during attacks which was mentioned earlier.

*Constipation.*—A somewhat unexpected finding was the fact that constipation was a definite complaint in all the cases except three. As shown in table 9, this had usually developed during the course of the disease, or when there had been long-standing constipation it was definitely aggravated by the present trouble. This finding corroborates the observations of others, notably Friedenwald and Cullen<sup>13</sup> and Kiefer. The latter, in his study of thirty-three cases of cancer of the pancreas seen at the Peter Bent Brigham Hospital, obtained a history of constipation in the majority of cases and, as in my observations, found that it occurred in cases in which jaundice was absent, thus ruling out lack of bile in the intestinal tract as a causative factor. This frequent complaint of constipation with other suggestive findings, such

TABLE 8.—*Nausea and Vomiting in the Cases Reported*

	Cases
Nausea and vomiting present.....	3
Nausea without vomiting .....	4
Neither nausea nor vomiting.....	9
	<hr/> 16

TABLE 9.—*Constipation in the Cases Reported*

	Cases
Constipation associated with present illness.....	7
Chronic constipation, increased during illness.....	4
Constipation alternating with diarrhea during illness.....	2
None mentioned .....	3
	<hr/> 16

as blood in the stools, loss of weight and occasionally indeterminate roentgen findings, led in several instances to an incorrect diagnosis of carcinoma of the colon.

*Loss of Weight.*—A history of appreciable loss of weight and usually a corresponding degree of weakness occurred quite as commonly as pain, although this symptom never appeared as the chief complaint. In fifteen cases there was a definite statement of loss of weight in the anamnesis, while in the remaining case no specific mention was made of this fact, although from the notes on the physical examination it undoubtedly had occurred (table 10). Considering the fact that the average duration of symptoms at the time of admission was five and seven-tenths months, it is quite obvious that the loss of weight is especially rapid and marked, amounting to an average of 5.25 pounds

13. Friedenwald, Julius, and Cullen, T. S.: Carcinoma of the Pancreas: Clinical Observations. *Am. J. M. Sc.* 176:31 (July) 1928.

(2.4 Kg.) per month in this series. Indeed, it is this rapid and progressive emaciation associated with the crises of pain that may suggest the correct diagnosis in a doubtful case. Of all the situations in which carcinoma may occur, it seems that in the pancreatic body it causes cachexia most rapidly.

*Duration of Symptoms.*—As mentioned earlier, from the onset of the first symptoms the disease tends to run a rapid and steady course. Table 11 summarizes the duration of symptoms. From this table it will be noted that the majority of the patients had noticed symptoms for less than six months. The longest period elapsing between the

TABLE 10.—*Loss of Weight in the Cases Reported*

	Cases
Definite history of loss of weight.....	15
Not recorded .....	1
	16
Greatest loss of weight.....	31.8 Kg.
Smallest loss of weight.....	4.5 Kg.
Average loss of weight.....	13.5 Kg.

TABLE 11.—*Duration of Symptoms in the Cases Reported*

	Cases
Less than 1 month.....	1
1 to 3 months .....	4
4 to 6 months .....	6
7 to 12 months .....	4
Not recorded .....	1
	16
Average duration of 5.7 months	

onset of symptoms and admission to the hospital was one year, while in one case the duration of the present illness was too indefinite to record.

#### PHYSICAL EXAMINATION

The general examination usually revealed an extreme degree of emaciation and in many instances a patient suffering from agonizing pain. Inspection of the abdomen showed that in four of the sixteen cases there was dilatation of the superficial veins of the abdominal wall, a finding suggesting some degree of obstruction of the vena cava. In exactly one half of the cases an abdominal tumor was palpable (table 12). As a rule, owing to the position of the pancreas, which is placed deep within the abdominal cavity, a tumor is not palpable until it has progressed to a rather advanced stage, and the findings at laparotomy almost invariably revealed a mass larger than had been expected from the clinical examination. Whether or not a palpable mass was

present, in the majority of cases there was abdominal tenderness of some degree. In no case in the series was there evidence of a distended gallbladder.

Fever was ordinarily absent. The temperature on admission in all of the sixteen cases was under 100 F.

TABLE 12.—*Results of Abdominal Examination in the Cases Reported*

	Cases
Palpable tumor .....	16
Present .....	8
Absent .....	8
Location of tumor .....	8
Right upper quadrant .....	1
Left upper quadrant .....	1
Midepigastrium .....	5
At umbilicus .....	1
Dilatation of superficial veins of abdomen .....	16
Noted .....	4
Not mentioned .....	12

#### LABORATORY FINDINGS

*Blood.*—In accord with the essentially normal temperature charts, the leukocyte count was less than 10,000 in fourteen of the cases and slightly over 10,000 in one case; in one case the count was not made.

TABLE 13.—*Laboratory Findings in the Cases Reported*

	Red Blood Cell Count	Hemoglobin, Percentage
Blood		
Erythrocytes		
Lowest .....	3,080,000	58
Highest .....	5,060,000	82
Average .....	4,400,000	75
		Cases
Leukocytes		
Over 10,000 .....		1
Under 10,000 .....		14
Not recorded .....		1
		16
Urine		
Glycosuria .....		2
Negative for sugar .....		14
		16
Stool		
Positive guaiac or benzidine test .....		4
Normal .....		4
Not examined .....		8
		16
Gastric Analysis		
Free hydrochloric acid present (after test meal) .....		4
Free hydrochloric acid absent .....		0
Examination not made .....		12
		16

No evidences of high grade anemia appeared, the lowest erythrocyte count in the group being 3,080,000, with a corresponding hemoglobin reading of 58 per cent. The highest erythrocyte count recorded was

5,060,000, with 82 per cent hemoglobin, while the highest hemoglobin determination was 95 per cent, with a corresponding erythrocyte count of 4,200,000. The average hemoglobin reading for the series was 75 per cent (table 13).

*Urine.*—Particular attention was paid to the examination of the urine for dextrose. Curiously enough, glycosuria was present in only two of the sixteen cases, in one of which there was a typical diabetic blood sugar curve. These figures are of interest in view of the fact that even though in many of the cases a large portion of the pancreatic substance was destroyed by the neoplasm, sufficient pancreatic tissue evidently remained to maintain a normal production of the internal secretion.

TABLE 14.—Roentgen Findings in the Cases Reported

	Cases
Lesion of colon (carcinoma?).....	1
Negative roentgen findings.....	5
Pyloric obstruction .....	2
Duodenal distortion or displacement.....	6
No roentgenograms taken.....	1
Indeterminate (lesion of stomach or duodenum).....	2
	<hr/> 16
Roentgenogram suggestive of pancreatic tumor.....	4

TABLE 15.—Clinical or Preoperative Diagnosis in the Cases Reported

	Cases
Carcinoma of the stomach.....	3
Carcinoma of the .....	5
Chronic duodenal .....	2
Gallstones .....	1
Benign (?) pyloric obstruction.....	1
Carcinoma of the colon.....	4
Tumor (cyst?) of the pancreas.....	1
Chronic appendicitis .....	1
	<hr/> 16

*Gastric Analysis.*—The results of gastric analysis were recorded in only four of the sixteen cases. In all four cases free hydrochloric acid was present in normal amounts, there being no instance of achlorhydria.

*Stools.*—The stools were examined in eight cases. Occult blood was present in four, and in the remaining four cases the examination revealed no abnormalities. None of the stools were clay-colored, and there was no record of the bulky, battery stools so often seen in carcinoma of the head of the pancreas with obstructive jaundice. It would seem from these findings that the external secretion of the pancreas in adequate amounts was reaching the intestinal tract, and presumably the greater part came from the cephalic portion of the gland.

*Roentgen Findings.*—Roentgen studies were made in all of the cases except one. Table 14 summarizes the findings. It is of interest that in four cases, or 25 per cent of the group, the roentgenologist suspected a lesion of the pancreas, this impression being gained chiefly from the distorted appearance of the duodenum or a widening of the normal duodenal curve.

*Clinical Diagnosis:* The clinical or preoperative diagnoses are tabulated in table 15. As will be noted, a correct diagnosis was made in three cases, and a diagnosis of pancreatic cyst in one other instance. The most common diagnosis erroneously made was carcinoma of the colon. This was largely due to the fact that the patients exhibited the general cachexia of cancer, with no clear evidence of a primary growth and often with a history of increasing constipation, frequently blood in the stool as shown by chemical tests and finally indeterminate results of roentgenologic studies. As roentgen diagnosis of lesions of the colon was far less accurate a few years ago than it is today, one felt justified in making a presumptive diagnosis of carcinoma of the colon under such circumstances.

#### OPERATION

Operation was performed in all of the cases except those of the two patients who died in the hospital; in these two cases the diagnosis was confirmed by necropsy. Table 16 lists the various operative procedures

TABLE 16.—*Operation in the Cases Reported*

	Cases
Exploratory laparotomy .....	7
Cholecystoduodenostomy .....	1
Cholecystogastrostomy .....	3
Posterior gastro-enterostomy .....	1
Posterior gastro-enterostomy and cholecystostomy .....	1
Marsupialization .....	2
No operation .....	2
	16

TABLE 17.—*Cell Type of the Tumor in the Cases Reported*

	Cases
Scirrhus adenocarcinoma .....	1
Adenocarcinoma .....	4
Medullary carcinoma .....	3
No report .....	8
	16

which were performed. At the time of operation, metastatic nodules were found in the liver in five cases and were absent in eleven cases. There was no evidence of ascites in thirteen of the sixteen cases, while ascitic fluid was encountered in three, in one of which it was distinctly

of the chylous type, a type often mentioned in the literature and indicative of obstruction of the thoracic duct.

In table 17 are shown the types of cancer as reported by the pathologist when biopsy specimens were taken, and table 18 summarizes the location of the lesions in the pancreas.

TABLE 18.—*Situation of Growth in the Cases Reported*

	Cases
Tail .....	2
Body .....	12
Body and tail.....	2
	<hr/> 16

# END-RESULTS

There were no deaths at operation. Of the fourteen patients operated on, six were discharged from the hospital unimproved, seven completely or partially relieved from pain and one definitely worse. In the group of patients who were relieved from pain there seemed to be no relation to the type of operation, and the improvement following simple exploratory laparotomy in some cases was as great as that following some of the more complicated procedures.

TABLE 19.—*End-Results in the Cases Reported*

	Patients
Died in hospital without operation.....	2
Not heard from.....	3
Lived 1 month.....	2
Lived 1½ months.....	1
Lived 2 months.....	2
Lived 2½ months.....	1
Lived 3½ months.....	1
Lived 10 months.....	1
Lived 18 months.....	1
Living at 6 months.....	1
Living at 9 months .....	1
	<hr/> 16

A questionnaire was sent out to determine the course following discharge from the hospital. In table 19, the end-results are tabulated. Of the eight cases in which operation was performed and in which the time of death was ascertained, the average duration of life following operation was four and five-tenths months. Since the average duration of symptoms prior to admission was five and seven-tenths months, the average duration of life in these cases was ten and two-tenths months from the time the first symptoms were noted. It might be added that in the two cases in which the patients died in the hospital without operation the duration of symptoms was eight months and one month, respectively.



## REPORT OF CASES

CASE 1.—M. S., a Canadian housewife, aged 61, was admitted to the University Hospital on April 4, 1926, with the complaint of pain in the stomach and diabetes. Symptoms had begun four months previously with a dull, aching pain in the left upper quadrant of the abdomen, associated with constipation and nausea without vomiting. The pain did not radiate; it was aggravated by food but was often relieved by soda. The patient had also noticed polyuria, polydipsia and pruritus vulvae. Six weeks before entrance a physician had discovered sugar in the urine. The patient had lost 76 pounds (34.5 Kg.) since the beginning of her trouble.

Examination showed evidence of extreme loss of weight. The abdomen was doughy, and there were tenderness and a questionable mass in the left upper quadrant, with slight muscle spasm in this area. The temperature was 98 F.; the pulse rate, 98, and the respiratory rate, 20. The blood pressure was 134 systolic and 82 diastolic. The urine had a specific gravity of 1.036 and contained sugar (+++). The Kahn test of the blood was negative. The blood sugar was 290 mg. per hundred cubic centimeters, and the nonprotein nitrogen of the blood, 29.6 mg. per hundred cubic centimeters. The blood count showed: leukocytes, 19,000, with 63 per cent polymorphonuclears; erythrocytes, 6,100,000 and hemoglobin, 70 per cent. The spinal fluid was normal. Roentgen examination showed a normal upper region of the gastro-intestinal tract, and the barium sulphate enema revealed a normal colon. The chest was emphysematous. The clinical diagnosis was disease of the gallbladder with pancreatitis or a malignant condition of the abdomen.

The diabetes was satisfactorily controlled by diet and insulin. Exploratory laparotomy was performed on May 20 by Dr. Collier, who made the following notes: A large, hard carcinomatous mass was felt in the body of the pancreas. There were metastases in the liver. The condition was thought to be hopeless.

The postoperative course was satisfactory, and there was some relief from the abdominal pain. The patient was discharged on June 15.

CASE 2.—A. B., a German housewife, aged 58, was admitted on April 19, 1926, complaining of pain in the stomach and back. The trouble began about one year before admission, with constipation and severe pain in the stomach at night. The pain gradually became more constant and severe and extended to the back. It was not related to food and was sometimes relieved by soda. The patient had lost 40 pounds (18.1 Kg.) during the illness.

Examination revealed a fairly well nourished woman crying from pain. There were dilatation of the superficial veins of the abdomen, exquisite tenderness and a palpable mass in the epigastrium. The blood pressure was 185 systolic and 85 diastolic. The temperature was 99.2 F.; the pulse rate, 100, and the respiratory rate, 24. The urine was normal. Examination of the blood revealed: leukocytes, 8,000, with 64 per cent polymorphonuclears; erythrocytes, 3,800,000, and hemoglobin, 65 per cent. Roentgenologic studies showed a stiff lesser curvature of the stomach without defect, suggestive of carcinoma of the lesser curvature, although the results of the examination were reported as indeterminate. The clinical diagnosis was carcinoma of the stomach.

Operation was performed on May 5 by Dr. Cabot, who found chylous turbid fluid in the abdomen. The stomach, duodenum, gallbladder and liver were normal. Behind the stomach a large mass was felt in the pancreas. It was fixed, stony hard and nodular and was thought to be a carcinoma of the body of the pancreas, with obstruction to the thoracic duct. A cholecystogastrostomy was done to avoid the possibility of obstructive jaundice later.

Postoperative convalescence was not remarkable, and the patient was discharged on June 1. She died on Aug. 23 of cachexia due to cancer, although she was completely relieved of pain and there was no jaundice up to the time of death.

CASE 3.—T. R., a French-Canadian painter, aged 50, was admitted on July 20, 1926, complaining of pain in the stomach and chronic constipation. Symptoms began six months previously with pain in the back, which soon shifted to the upper part of the abdomen and often radiated to the right shoulder and the hips. The pain was worse at night, was increased by food and was never relieved by soda. The patient had lost 60 pounds (27.2 Kg.) during the present illness.

Examination showed a pale, very ill, cachectic man. There was a tender mass the size of an orange just above the umbilicus, and an area of tenderness was present in the left lower quadrant of the abdomen. The blood pressure was 145 systolic and 90 diastolic; the temperature, 98 F.; the pulse rate, 68, and the respiratory rate, 18. The leukocytes numbered 8,800, with 61 per cent polymorphonuclears, and the erythrocytes, 4,400,000; the hemoglobin content was 70 per cent. The urine was normal. The reaction to the benzidine test of the stool was + + + +. Roentgen examination showed distortion of the duodenum suggesting enlargement of the pancreas. The Graham test showed slight evidence of chronic cholecystitis. A barium sulphate enema revealed no abnormalities. Pycnograms showed an extrarenal tumor. The clinical diagnosis was carcinoma of the pancreas or pancreatic cyst.

Exploratory laparotomy was performed on August 23 by Dr. Collier, and the following observations were made: A large mass was felt posterior to the stomach which pushed the stomach forward. The liver, gallbladder, stomach and intestines were normal. The body of the pancreas was completely involved by the mass, which was apparently a carcinoma. It was so extensive that no attempt was made to remove it. There were no metastases except one palpable gland in the lower part of the abdomen.

Postoperative convalescence was uneventful, and the patient was discharged from the hospital on September 7.

CASE 4.—S. W., Polish factory worker, aged 49, was admitted on Aug. 20, 1926, complaining of pain in the right upper quadrant of the abdomen and in the back. Symptoms began two months before his entry, with the gradual onset of abdominal pain which rapidly became more severe and constant. It was much worse at night but did not seem to be related to meals or to food. Nothing that he had tried for its relief was successful. He had lost 12 pounds (5.4 Kg.).

Examination showed a poorly nourished, pale man in considerable pain. There was dilatation of the superficial veins of the abdomen, and a palpable mass, possibly the liver, was felt in the right upper quadrant. There was marked tenderness in the region of this mass with moderate right costovertebral tenderness. The blood pressure was 142 systolic and 88 diastolic. The temperature was 99 F.; the pulse rate, 99, and the respiratory rate, 20. The urine showed albumin and a few casts. Examination of the blood revealed: leukocytes, 7,600, with 82 per cent polymorphonuclears; erythrocytes, 4,400,000, and hemoglobin, 85 per cent. The roentgen examination revealed the following: The barium sulphate enema revealed no abnormalities, and the films of the gastro-intestinal tract showed slight deformity of the duodenal bulb on the side of the greater curvature, but the conclusions were indeterminate. The Graham test showed a gallbladder which functioned normally. The clinical diagnosis was carcinoma of the stomach, chronic cholecystitis or carcinoma of the hepatic flexure.

Exploratory laparotomy was performed on August 25 by Dr. Cabot, who made the following notes: The gallbladder was found somewhat thickened and adherent.

The liver was full of carcinomatous nodules, clearly metastatic. The stomach, intestines and colon were normal. The pancreas seemed infiltrated, particularly at its splenic end, and it seemed probable that the lesion was primarily a cancer of the pancreas with metastases to the liver.

Microscopic examination of the biopsy specimen showed diffuse adenocarcinoma.

Postoperative convalescence was uneventful, and the patient was discharged from the hospital on September 8. He died in November, jaundice having developed before death.

CASE 5.—F. L., an American laborer, aged 69, was admitted on Feb. 9, 1927, complaining of attacks of colicky midepigastria pain and constipation. The attacks usually lasted for from one to two hours, causing the patient to double up. They were unrelated to food. There was no history of associated nausea or vomiting. There had been considerable loss of weight, but the patient did not know how much.

Examination showed an elderly, poorly nourished man with his knees drawn up, writhing in pain. There was considerable sclerosis of the peripheral arteries. The blood pressure was 122 systolic and 98 diastolic; there was dilatation of the superficial veins of the abdomen; muscle spasm and tenderness were present in the right upper quadrant, and there was moderate generalized abdominal tenderness. The temperature was 98 F.; the pulse rate, 80, and the respiratory rate, 20. The urine was normal. The Wassermann test of the blood was negative. The leukocyte count was 4,500, with 74 per cent polymorphonuclears; the erythrocyte count, 3,500,000, and the hemoglobin content, 65 per cent. The guaiac test of the stool gave negative results. Roentgen studies of the stomach showed hyperperistalsis and constant deformity at the pyloric ring with 50 per cent retention in six hours. The impression was that a surgical lesion was obstructing the pylorus. The barium enema showed no abnormalities. The clinical diagnosis was carcinoma of the pylorus.

Operation was performed on February 15 by Dr. Cabot, whose observations follow: There was free fluid in the abdomen, with dilated veins suggesting portal obstruction. At a point apparently beyond the pylorus the stomach was obstructed by a mass which appeared to be behind the stomach and in relation to the pancreas. The gallbladder was slightly distended and tense. The liver was free from metastases. There was a soft mass 2 inches (5.08 cm.) in diameter in the mesentery of the transverse colon. Removal seemed impossible. A posterior gastro-enterostomy was therefore done and the gallbladder drained to anticipate the possibility of future obstruction of the biliary tract.

Postoperative convalescence was satisfactory, and on March 7 the patient was discharged from the hospital. He died at home one month later.

CASE 6.—J. W., an American nightwatchman, aged 63, was admitted on Dec. 16, 1927, complaining of epigastric distress of six months' duration. At first he had noticed a dull ache or heavy sensation in the epigastrium, which was made worse by food. In addition, there had been extreme tenderness over the entire abdomen so that at times he could not bear the pressure of his clothing. There had also been severe constipation with occasional periods of diarrhea and some difficulty in swallowing. The patient had lost 9 pounds (4.1 Kg.).

Examination revealed marked emaciation, dilatation of the superficial veins over the lower part of the abdomen and tenderness over the right half of the abdomen particularly marked in the right upper quadrant. There was slight muscle spasm but no palpable mass. The blood pressure was 130 systolic and 80 diastolic. The temperature was 99 F.; the pulse rate, 90, and the respiratory rate, 20. The laboratory studies showed normal urine, a leukocyte count of 9,100 and a hemoglobin

content of 78 per cent. Roentgen examination of the stomach showed hyperperistalsis. There was great dilatation of the duodenal bulb but no evidence of ulcer. The intestines were otherwise normal. The entire colon was dilated, but there was no evidence of a pathologic condition. There was spina bifida occulta. The clinical diagnosis was chronic duodenal ileus, of unknown cause (cancer?).

Laparotomy was performed on December 27 by Dr. Cabot, who made the following notes: The stomach was not abnormal. The duodenum showed great distention practically throughout. The gastrohepatic omentum showed some enlarged, hard glands. Below this the pancreas appeared to be abnormally hard and was felt in the neighborhood of the ligament of Treitz, where it might possibly have caused obstruction. The large intestine showed abnormal distention, but examination failed to show any abnormality other than that a fair amount of intestinal contents was unevacuated. The gallbladder was moderately distended and free from adhesions and showed no evidence of inherent abnormality. There seemed to be no clear indication for gastro-enterostomy. The gallbladder was anastomosed to the first portion of the duodenum, to which it came without difficulty.

The postoperative course was fair. The appetite was poor, and there were troublesome pains due to gas. The patient was discharged from the hospital on Jan. 14, 1928, and died on February 22.

CASE 7.—E. H., an American housewife, aged 41, was admitted on April 11, 1928, complaining of pain in the stomach. Symptoms began three weeks before her admission to the hospital, with an attack of sharp, knifelike pain in the epigastrium. The pain radiated to the back and up the spine and localized between the shoulder blades. There were repeated attacks with accompanying nausea and vomiting. Later the pain became constant. There had been increasing constipation after the onset of the other symptoms. The patient had lost 10 pounds (4.5 Kg.).

Examination revealed an emaciated woman who appeared to be elderly. There was a large tumor in the midline of the upper part of the abdomen; it was globular in outline and extended from just below the xiphoid to one fingerbreadth below the umbilicus. The mass had a diameter of 12 cm. and was firm; the surface was smooth. The mass seemed to be attached to the underlying structures. It was slightly tender to palpation. The blood pressure was 130 systolic and 84 diastolic; the temperature, 98.6 F.; the respiratory rate, 20, and the pulse rate, 90. The laboratory studies showed normal urine, a leukocyte count of 6,700, an erythrocyte count of 3,080,000, a hemoglobin content of 58 per cent and a negative Kahn test of the blood. The Graham test by roentgen rays showed normal visualization of the gallbladder, with normal emptying after a meal of fat. The clinical diagnosis was solid tumor or cyst of the pancreas. Exploratory laparotomy was performed on April 14 by Dr. Cabot, whose observations follow: The tumor was found to lie behind the stomach, which was in no way involved. It was clearly of the pancreas and was very hard, showing no evidence of cystic qualities in any part. There was no evidence of obstruction of the biliary passages, and the gallbladder appeared to be normal. There were a reasonably large number of glands in the neighborhood, apparently involved; one of them lying in the transverse mesocolon was removed for pathologic examination.

Microscopic examination of the biopsy specimen by Dr. C. V. Weller showed a rapidly growing metastatic medullary carcinoma of a lymph node; there were many mitotic figures.

Postoperative convalescence was not very satisfactory; there was considerable leakage of ascitic fluid from the wound, and the patient's condition gradually

became worse. She was discharged from the hospital on April 27 and died at home one month later.

CASE 8.—C. N., a Swedish machinist, aged 60, was admitted on April 14, 1930, complaining of stomach trouble. The symptoms began four months prior to admission, with loss of appetite and malaise. This was soon followed by epigastric distress and eructations of gas. The patient vomited about once a day and was relieved by gastric lavages and by alkalis. There was then a period of several weeks of comparative freedom from pain until three weeks before admission, when the pain recurred with increased severity but without vomiting. On admission the patient was suffering from severe epigastric pain and gas. He had lost 30 pounds (13.6 Kg.).

Physical examination revealed moderate abdominal distention with visible peristalsis but no masses. The blood pressure was 130 systolic and 94 diastolic; the temperature, 99 F.; the respiratory rate, 20, and the pulse rate, 80. The urine was normal. The Kahn test of the blood was negative. The leukocyte count was 7,700, with 79 per cent polymorphonuclears; the erythrocyte count, 5,060,000, and the hemoglobin content, 82 per cent. Examination of the stool revealed a ++++ reaction to the benzidine test. Roentgen studies revealed a large dilated stomach with gigantic peristaltic waves; 70 per cent retention at four hours, 50 per cent retention at twenty-four hours, and marked retention at forty-eight hours, and an obstructive lesion at the pyloric end of the stomach of surgical importance. The clinical diagnosis was pyloric obstruction, probably benign.

Operation was performed by Dr. Cabot on April 23, and his operative note follows: Examination of the stomach showed no discoverable abnormality other than great hypertrophy. The pylorus appeared to be dilated. On the posterior wall of the second portion of the duodenum was a hard, nodular mass apparently implanted in the wall. This seemed to be intimately connected with a tumor which occupied the greater part of the pancreas except the head. There was slight dilatation of the gallbladder. A gland was removed from the region for diagnosis, and a posterior gastro-enterostomy was performed to relieve the obstruction in the second portion of the duodenum.

Microscopic examination of the biopsy specimen by Dr. A. S. Warthin showed only chronic lymphadenitis.

The postoperative course was satisfactory, and the patient was discharged from the hospital on May 8. He returned to the clinic on November 19, complaining of great weakness, pain in the epigastrium, poor appetite and constipation. His symptoms had been much relieved following the operation until October 1930. After that he lost considerable weight; there was a large mass in the epigastrium, and the edge of the liver was 5 fingerbreadths below the margin of the ribs. He died on Feb. 22, 1931, in a condition of extreme emaciation. Jaundice had developed two months before death.

CASE 9.—N. S., a German barber aged 40, was referred to the radiotherapy department of the University Hospital on Aug. 28, 1930, for postoperative treatment. Symptoms had begun three months previously with slight pain in the right lower quadrant of the abdomen which lasted for three days and then disappeared. Since the onset there had been repeated attacks of pain in this region. One month prior to entry the patient experienced a severe, cramping pain in the right lower quadrant. It continued for two days, a mass appearing in the abdomen while the pain continued.

A diagnosis of appendicitis was made, and operation was performed on July 25 in a neighboring hospital. The surgeon who performed the operation stated that a tumor the size of an orange presented through the gastrocolic omentum and

seemed to take origin from the body of the pancreas. The tumor was cystic, the fluid contents being bloody. It was evacuated, and marsupialization was done, a drainage tube being inserted. No metastases were found. A biopsy specimen of the tumor examined by Dr. A. S. Warthin showed that it was an undifferentiated medullary carcinoma.

Physical examination showed a fairly recent scar left by a right rectus incision. There was a nontender, slightly irregular, slightly movable mass about the size of a large grapefruit at or just above the umbilicus. Near the lower end of the surgical scar a draining sinus extended into the tumor. From it there was a small amount of seropurulent discharge. The temperature was 99.2 F.; the pulse rate, 88, and the respiratory rate, 20. The laboratory studies revealed normal urine except for many hyaline casts, a negative Kahn test of the blood, a leukocyte count of 9,200 and a hemoglobin content of 79 per cent. The results of roentgen examination were as follows: The Graham test showed a normally functioning gallbladder. There was distortion of the second portion of the duodenum suggesting enlargement of the pancreas.

The patient was given roentgen treatments as an outpatient. He died on Feb. 8, 1932, of cachexia due to cancer.

CASE 10.—M. C., a Canadian housewife, aged 69, was admitted on Nov. 3, 1930, complaining of pain in the right side of the abdomen. Symptoms had begun suddenly four weeks previously with pain in both the right upper and the right lower quadrant, radiating to the right costovertebral angle. Occasionally the pain radiated to the left upper quadrant and the left costovertebral angle. At first the pain was sharp, but it had gradually become dull and constant. There were gaseous eructations, the appetite was poor, and there was occasional nausea with vomiting. There had been chronic constipation for many years and this had become worse with the onset of the present trouble. The patient had lost 35 pounds (15.9 Kg.).

Physical examination revealed an elderly woman showing considerable evidence of loss of weight. There was tenderness in the right upper and right lower quadrants but no palpable mass. The blood pressure was 216 systolic and 120 diastolic; the temperature, 99 F.; the pulse rate, 100, and the respiratory rate, 22. The urine was normal except for a + reaction for albumin. The Kahn test of the blood was negative; the nonprotein nitrogen content was 31 mg. per hundred cubic centimeters; the leukocyte count was 8,900, with 65 per cent polymorphonuclears; the erythrocyte count, 3,670,000, and the hemoglobin content, 70 per cent. Examination of the stool revealed a + reaction to the benzidine test. Roentgen studies were made in another hospital shortly before admission and gave negative results except for slight flattening of the cecum. Roentgenograms of the gastrointestinal tract made at this hospital gave entirely negative results, the barium enema showed nothing abnormal and the Graham test was unsatisfactory.

On November 3 the patient was transferred from the medical to the surgical department for an exploratory laparotomy, the clinical diagnosis being carcinoma of the colon. Bronchopneumonia developed, and the patient died on November 8. Necropsy performed by Dr. Bugher on that day showed primary adenocarcinoma of the body of the pancreas, bilateral acute confluent lobular fibrinopurulent pneumonia and terminal cardiac failure.

CASE 11.—W. D., an unemployed American man, aged 63, was admitted on Dec. 15, 1930, complaining of pain in the abdomen and increasing constipation. The symptoms had begun eight months previously with an attack of severe colicky pain about the umbilicus. The pain was excruciating and recurred daily without relation to meals and unaccompanied by nausea or vomiting. It often radiated

around the right flank to the back and sometimes down the right leg. The attacks lasted from a few minutes to half an hour, and the pains seemed to be worse when constipation was most marked. There had been a loss of 30 pounds (13.6 Kg.) in eight months, with corresponding weakness. The patient had been troubled for several years with increasing constipation.

Physical examination showed a fairly well preserved elderly man. The abdomen was distended, the edge of the liver was palpable and a mass the size of an orange was present in the midepigastriac region. The mass was moderately tender. There was considerable sclerosis of the peripheral arteries; the blood pressure was 158 systolic and 92 diastolic; the temperature, 99 F.; the pulse rate, 92, and the respiratory rate, 20. The urine was normal, with the gravity as determined by the concentration test up to 1.026; the excretion of phenolsulphonphthalein was 65 per cent in two hours. The Kahn test of the blood was negative. The blood sugar during fasting was 103 mg., and the nonprotein nitrogen, 33 mg. per hundred cubic centimeters; the bilirubin was 3 mg. per thousand cubic centimeters. The leukocyte count was 9,000, with 66 per cent polymorphonuclears; the erythrocyte count, 4,000,000, and the hemoglobin content, 74 per cent. The electrocardiogram showed slight left ventricular preponderance. Roentgen studies revealed a steer-horn stomach; the second portion of the duodenum showed a tendency to looping, with a constant pattern noticed on all the films such as is sometimes seen in enlargement of the head of the pancreas. The barium enema revealed no evidence of an organic pathologic condition or other abnormality. A clinical diagnosis of carcinoma of the colon was made.

The patient's general condition was too poor to permit an exploratory laparotomy. He died on March 20, 1931. Autopsy was performed by Dr. C. V. Weller on March 21. He found primary scirrhous carcinoma of the tail of the pancreas; metastases in the liver, suprarenals, retroperitoneal lymph nodes, sternum and vertebrae, with infiltration of the spinal nerves; pulmonary embolism, and multiple infarcts of the spleen.

CASE 12.—C. S., an American railroad man, aged 50, was admitted on Jan. 26, 1931, complaining of boring epigastric pain. His symptoms had begun five months previously, with gaseous eructations and a sour taste in the mouth, followed by the development of the midepigastriac pain, which was constantly present but worse after eating. There was slight relief from milk or soda. The patient's appetite was good, but he was afraid to eat. There had been increasing constipation over the past few years. He did not complain of nausea or vomiting. He had lost 35 pounds (15.9 Kg.).

Examination showed a slightly undernourished, worried, middle-aged man. There was exquisite tenderness in the epigastrium and the right upper quadrant, accompanied by slight muscle spasm but no palpable mass. The blood pressure was 115 systolic and 70 diastolic; the temperature, 99; the pulse rate, 80, and the respiratory rate, 20. The urine was normal. The leukocyte count was 8,100, with 60 per cent polymorphonuclears; the erythrocyte count, 4,540,000, and the hemoglobin content, 80 per cent. The Kahn test of the blood was negative. The guaiac test of the stool gave negative results. Roentgenologic examination showed a defect in the prepyloric region (neoplasm or ulcer?). The Graham test showed nonvisualization of the gallbladder. The clinical diagnosis was carcinoma of the stomach or carcinoma of the pancreas.

Operation was performed by Dr. Ransom on February 9, and his note was as follows: The gallbladder was slightly distended; there was a small amount of free fluid in the abdomen, and the stomach, duodenum and liver were normal. There was an irregular hard, nodular mass behind the stomach and in the pancreas,

undoubtedly carcinoma. This extended to the left, involving the tail of the organ. A biopsy was not thought feasible, and cholecystogastrostomy was done to anticipate the possibility of obstruction of the biliary tract.

The postoperative course was rather stormy; there were considerable nausea and vomiting for the first week, and this was followed by bronchopneumonia on the right side from which the patient recovered satisfactorily. He was discharged on February 26 and placed on a Sippy diet. The pathologic report on a bit of the gallbladder removed at the time of operation showed that the wall of the gallbladder was normal. Following the patient's discharge from the hospital he was given several treatments with high voltage roentgen rays and was last seen on April 10, at which time there was marked epigastric pain as well as marked loss in weight and general deterioration.

CASE 13.—J. S., a Canadian factory worker, aged 62, was admitted on Feb. 27, 1932, complaining of constipation, gas and pain in the upper part of the abdomen and the lower part of the back. His symptoms had begun one year before, although there had been trouble from constipation for about eight years. During the preceding year there had been a steady loss of approximately 25 pounds (11.4 Kg.). There had been considerable anorexia during this year. For the three months prior to entry, there had been a constant dull pain in the lower part of the abdomen. Later this had become sharp and shooting and had radiated through to the back. These sharp, colicky pains ordinarily lasted for several hours, but the constant abdominal distress never disappeared. The colicky pains were often relieved by bowel movements.

Physical examination showed an elderly emaciated man, appearing quite ill. The abdominal examination gave negative results. The blood pressure was 180 systolic and 20 diastolic; the temperature, 98.6 F.; the pulse rate, 92, and the respiratory rate, 24. Laboratory examinations revealed normal urine, a negative Kahn test of the blood, a leukocyte count of 5,300 and a hemoglobin content of 76 per cent. Roentgen examination showed an obstructing lesion of the ascending colon. A preoperative diagnosis of carcinoma of the ascending colon was made.

Dr. Collier operated on February 29 and made the following notes: The body of the pancreas was 8 cm. in width and hard and thickened. The condition seemed to be characteristic of carcinoma. The right lobe of the liver was studded with carcinomatous nodules. A nodule was present in the wall of the hepatic flexure; there was one nodule in the abdominal wall, and still others were present in the transverse mesocolon. There was not enough obstruction to the colon to warrant colostomy.

The microscopic examination of the biopsy specimen was reported on as follows: The bit of tissue (mesentery?) showed infiltration by adenocarcinoma. The carcinoma occurred in the form of small nests lined by high columnar epithelium and showed a fair degree of differentiation.

Postoperative convalescence was satisfactory, and the patient was discharged to the Convalescent Hospital on March 8 and was subsequently discharged to his home. He died on April 17.

CASE 14.—G. S., a Scotch farmer, aged 65, was admitted on June 17, 1932, complaining of a lump in the abdomen. Symptoms had begun three months previously with pain in the lower part of the abdomen and constipation. Six weeks before entry he had noted a mass in the epigastrium. There was considerable nausea but no vomiting. The pain was dull, aching and almost constant. The patient had lost 30 pounds (13.6 Kg.).

Examination revealed an anemic, undernourished elderly man not acutely ill. There was a palpable mass 7.5 by 5 cm. in the region of the umbilicus and extend-



ing upward from 3 to 4 cm. The mass was firm to palpation, quite tender and firmly fixed. No muscle spasm was present. The blood pressure was 135 systolic and 90 diastolic; the temperature, 98 F.; the pulse rate, 88, and the respiratory rate, 20. The laboratory studies revealed normal urine; a negative Kahn test of the blood; a leukocyte count of 4,000, and a hemoglobin content of 75 per cent. Roentgen examination after a barium enema revealed nothing abnormal. Roentgenograms of the gastro-intestinal tract gave negative results except for evidence of an extra-alimentary mass circumscribed by the third portion of the duodenum, probably a malignant cyst of the tail of the pancreas. A clinical diagnosis of cancer of the pancreas was made.

Dr. Collier performed an operation on June 18 and made the following observations: The entire body of the pancreas was the site of a carcinoma which was about 7 cm. in width, involving the entire pancreas except the head. It was firm, nodular and fixed. The right lobe of the liver contained several metastatic nodules varying from 1 to 5 cm. in diameter. The gallbladder was somewhat enlarged. Several lymph nodes along the border of the gastrohepatic omentum were enlarged. The common duct was not enlarged.

A biopsy specimen taken from the liver was reported as being medullary carcinoma; there was nothing in the specimen to show whether the condition was primary in the liver or metastatic.

The postoperative course was uneventful, and the patient was discharged from the hospital on June 27. He died on August 2. Jaundice had developed a short time prior to his death.

CASE 15.—E. C., an American railroad clerk, aged 56, was admitted on May 24, 1933, complaining of pain in the abdomen, chest, shoulder blades and legs. The symptoms had begun two years previously with pain of a throbbing type in the lower extremities, for which morphine had been required ever since. The abdominal pain began one year before entry and at first was sharp and shooting, later becoming constant, dull and throbbing. It often radiated to the back and shoulders. The patient complained of shortness of breath, gas and constipation. The pain was especially severe at night, so as seriously to interfere with sleep. The patient believed that there had been a slight loss of weight, but he was not clear as to the exact amount.

Physical examination showed a middle-aged man suffering from agonizing abdominal pain. The abdominal examination gave normal results. The blood pressure was 190 systolic and 100 diastolic; the temperature, 99 F.; the pulse rate, 80, and the respiratory rate, 20. The urine contained sugar (+). The Kahn test of the blood was negative. The leukocyte count was 9,600, with 72 per cent polymorphonuclears; the erythrocyte count, 3,000,000, and the hemoglobin content, 64 per cent. Examination of the stool revealed a ++ reaction to the benzidine test. Roentgen examination showed a definite intrinsic lesion of the proximal portion of the duodenum with partial obstruction, the exact nature of which could not be determined. The clinical diagnosis was duodenal neoplasm with obstruction.

Operation was performed by Dr. Potter on June 10, who made these observations: The liver was small and normal. The gallbladder was small and contracted and contained stones. In the second portion of the duodenum was a nodular mass situated posteriorly which on careful exploration by incision of the peritoneum over the retroperitoneal part of the duodenum seemed to be primarily in the pancreas. The mass was from 8 to 10 cm. in diameter, with extension upward into the regional lymph nodes and encroachment on the duodenum. There was mild dilatation above this mass but no evidence of obstruction of the biliary system.

No palliative procedure was thought advisable. A small bit of the pancreas in the neighborhood of the tumor was removed for biopsy.

The microscopic report on the biopsy specimen was adenocarcinoma, apparently early.

The postoperative course was uneventful. There was much less pain after operation than the patient had had previously. He was discharged from the hospital on June 22. In a letter dated March 6, 1934, he stated that he felt considerably better for a few weeks after returning home, but that the pain had increased in severity, being present in the back, arms, legs and abdomen.

CASE 16.—I. H., an American housewife, aged 66, was admitted on Aug. 9, 1933, complaining of attacks of sharp epigastric pain and constipation. Symptoms had begun six months previously with attacks of pain in the right upper quadrant occurring every night and lasting from three to six hours; they were associated with nausea but no vomiting. There was residual soreness with dull, constant pain between attacks. The pain often radiated to the back and gradually involved both the left upper and the left lower quadrant. The appetite had been poor, and there was troublesome constipation. There had been a loss of 20 pounds (9 Kg.).

Physical examination showed a moderately obese middle-aged woman, obviously in severe pain. The abdominal examination showed epigastric tenderness extending into the left upper quadrant but no mass or muscle spasm. The blood pressure was 148 systolic and 94 diastolic; the temperature, 99 F.; the pulse rate, 88, and the respiratory rate, 20. The laboratory studies revealed normal urine, a negative Kahn test of the blood; a leukocyte count of 12,600, with 67 per cent polymorphonuclears; an erythrocyte count of 4,350,000, and a hemoglobin content of 80 per cent. Examination of the stool gave negative results. An electrocardiogram gave negative results on two occasions. Roentgen examination showed hypertrophic arthritis of the spine; the Graham test showed a large, normal gallbladder emptying after a meal of fat and giving no evidence of stone. Roentgenograms of the gastro-intestinal tract and examination after a barium enema showed no positive organic lesion of the colon and no lesion of the upper alimentary tract. There was no evidence of renal calculi. The clinical diagnosis was carcinoma of the body of the pancreas or gallstones.

Operation was performed on September 15 by Dr. Ransom, who made the following notes: The gallbladder was slightly distended. In the body of the pancreas a large hard, fixed nodular mass was felt. The common duct was entirely normal. There were no metastases. The liver was normal. A cholecystogastrostomy was done to anticipate future obstruction of the biliary tract.

The postoperative course was uneventful, and the abdominal pain practically disappeared. The patient was discharged from the hospital on October 4. A follow-up note dated March 9, 1934, stated that the pain had returned with increased severity; it was greatly aggravated by bowel movements.

#### SUMMARY

Sixteen cases of carcinoma of the body or tail of the pancreas verified by operation or necropsy have been reviewed.

The incidence regarding age and sex is similar to that reported for carcinoma of the pancreas in general. The average age of the patients in this group was 57 years, and there were approximately twice as many men as women.

The symptomatology is characterized by severe pain, frequently occurring in crises, rapid and extreme emaciation and complete absence of jaundice.

An abdominal tumor was palpable in exactly one half of the cases.

Laboratory studies were of little assistance in arriving at a correct diagnosis.

Roentgen studies suggested the diagnosis in one fourth of the cases.

Clinically carcinoma of the body of the pancreas was mistaken for carcinoma of the colon more frequently than for any other single condition.

The average duration of life following operation was four and seven-tenths months, or ten and two-tenths months from the time symptoms were first noticed.

Various forms of surgical operation frequently afforded temporary relief from symptoms, but pain generally recurred before the time of death.

— 141 —

# SLIPPING OF THE PROXIMAL FEMORAL EPIPHYSIS

THERAPEUTIC RESULTS IN ONE HUNDRED AND ONE CASES

MAURICE M. POMERANZ, M.D.

AND

MARIAN FRAUENTHAL SLOANE, M.D.\*

NEW YORK

Much has been written regarding slipping of the proximal femoral epiphysis or the so-called epiphysiolysis. The literature in the main consists of case reports and deals with diagnostic or etiologic criteria rather than with treatment.

The therapeutic maneuvers which are recommended are designed essentially to realine the femoral head by either conservative or operative methods and to encourage its union to the neck by immobilization or rest. Unfortunately, inadequate follow-up histories are given in many of the cases reported, so that the reader is often unable to determine the value of the methods suggested. Despite the experience which was derived from the treatment of over 147 patients and which was reported in recent periodicals, there is still no unanimity of opinion regarding the most effective method of correction.

This study is prompted by a desire to determine the end-results of cases in which the patients were treated for this condition by various accepted methods and observed over a period of years. It seems particularly appropriate for the roentgenologist, as an unbiased agent, to do this, since his department is the medium in which most of the cases circulate and in which comparison of the various methods employed is possible. The roentgenogram follows the lesion from its inception to its termination.

In the pursuit of any activity there comes a time when it seems advisable to pause and take inventory. What is the objective? By what means does one seek to attain it? What has one accomplished? In the disease in question the time seems propitious for this self-examination. It is only in this manner and by this method that one can profit by one's failures, sharpen one's surgical judgment and improve one's technic. Stated differently, the proposition is: Given a disease with a known

---

\* Fellow, Henry W. Frauenthal Scholarship.

From the Department of Roentgenology, Hospital for Joint Diseases.

Read before the Section on Orthopedic Surgery, New York Academy of Medicine, March 16, 1934.

deformity and given a method or methods for its correction, the end-results justify the means employed. The consideration of methods is the purpose of this communication, and the justification of the methods will be obvious from the data submitted.

#### REVIEW OF THE LITERATURE

Wilson<sup>1</sup> reported the cases of 7 patients with epiphysiolysis treated at the Massachusetts General Hospital by surgical realinement of the head. Of this number, 2 patients had slight slipping and 5 had marked slipping; in 3 of the latter the bones had previously united in malposition. Wilson secured good operative results, with the exception of a slight limitation of flexion and shortening of the extremity varying from  $\frac{1}{4}$  to 1 inch (0.6 to 2.5 cm.).

Key's<sup>2</sup> excellent summary of the subject includes reports on 24 patients. Good results were obtained in the cases of 2 untreated adult patients and of 4 children for whom casts or braces were employed. There were poor results in 7 cases in which manipulation was used and in 1 case in which surgical realinement of the head was employed; in this eighth case an ankylosing arthritis followed the treatment. The 9 other cases were not followed up for end-results. Five cases were in older persons who were operated on for the correction of coxa vara deformities, and it is of interest to note that 1 of these patients died of infection.

Balensweig<sup>3</sup> reported 18 cases, in 2 of which the process was bilateral. Six patients showed slight slipping, and the remaining 14, marked slipping. Three patients with slight slipping were followed up for end-results. One untreated patient and 1 patient treated by immobilization in a cast had an excellent result, and 1 patient treated by manipulation had a fair result. Ten patients with marked slipping were followed up. For 8, manipulation had been used; a bad result followed in 6 cases, a fair result in 1 case and an excellent result in 1 acute case. In the remaining 2 cases operations were performed; in 1 a bad result followed the removal of a wedge from the epiphyseal line, and in the other the end-result was fair, but the type of operation was not stated.

Bernstein and Arens<sup>4</sup> reported 6 cases, in 2 of which the condition was bilateral. Of the 3 cases followed up, a fair result was obtained

1. Wilson, P. D.: Displacement of Upper Epiphysis of Femur Treated by Open Reduction, *J. A. M. A.* **83**:1749 (Nov. 29) 1924.

2. Key, J. A.: Epiphyseal Coxa Vara or Displacement of Capital Epiphysis of Femur in Adolescence, *J. Bone & Joint Surg.* **8**:53 (Jan.) 1926.

3. Balensweig, L.: Femoral Osteochondritis of Adolescence and Sequelae, Epiphyseal Separation of Hip, *Surg., Gynec. & Obst.* **43**:604 (Nov.) 1926.

4. Bernstein, M. A., and Arens, R. A.: Epiphyseolysis, *Radiology* **9**:497 (Dec.) 1927.

in 2 cases in which the patient was not treated, and a good result in an acute case in which manipulation with replacement had been resorted to within two days of the onset.

Smith<sup>5</sup> reported 2 cases of bilateral slipping in which the patient was treated by manipulation with good results.

Badgley<sup>6</sup> reported 27 cases, in 5 of which the slipping was lateral. Of 19 cases in which manipulation was employed, there were good results in 9, fair results in 1 and poor results in 9. Subsequently in 5 of these cases in which the results were unsatisfactory surgical relinement of the head was resorted to. Nonunion resulted in 2 cases, fibrous ankylosis in good position in 1 case and fibrous ankylosis in poor position in another case; the period of observation of the fifth case was too short to enable one to estimate the end-result. In the 2 remaining cases a Whitman reconstruction operation was performed. In 1 the result was favorable; in the other ankylosis of the hip developed.

Willis<sup>7</sup> gave the end-results for 12 of his 15 patients. He employed casts in 6 cases, with satisfactory results, but he failed to mention the instances of manipulation prior to their use. He employed braces in 3 cases, with fair results in 2 and failure in 1, in which a subsequent oblique osteotomy of the neck of the femur resulted poorly. In the 1 case in which he employed manipulation successfully the patient showed secondary arthritic changes within a short time. Willis obtained good results in 4 cases in which operation was resorted to; in 1 case previous manipulation had failed to help. Unfortunately, he did not state the type of operation performed.

In his article on injuries about the hip joint Johnson<sup>8</sup> presented roentgenograms taken in a case of acute traumatic separation in which the defect was slightly overcorrected by traction and abduction but in which there was perfect function within three months.

Jahss<sup>9</sup> successfully treated 3 patients by a new method of non-surgical reduction. He converted the condition into one of acute fracture by forceful manipulation; this procedure was followed by immobilization in plaster casts. He<sup>10</sup> obtained good results later in the preslipping

5. Smith, M. K.: Epiphyseal Coxa Vara, *Am. J. Surg.* 5:387 (Oct.) 1928.

6. Badgley, C. E.: Displacement of Upper Femoral Epiphysis: Summary of Twenty-Seven Studied Cases, *J. A. M. A.* 92:355 (Feb. 2) 1929.

7. Willis, T. A.: The Slipping Femoral Epiphysis, *J. Bone & Joint Surg.* 11:779 (Oct.) 1929.

8. Johnson, H. F.: Unusual Bony Injuries About the Hip Joint, *Surg., Gynec. & Obst.* 49:630 (Nov.) 1929.

9. Jahss, S. A.: Displacement of the Upper Epiphysis of the Femur (Adolescent Coxa Vara): Treated by Closed Reduction, *J. Bone & Joint Surg.* 13:856 (Oct.) 1931.

10. Jahss, S. A.: Slipping of the Upper Femoral Epiphysis: Treatment in the Pre-Slipping Stage, *J. Bone & Joint Surg.* 15:477 (April) 1933.

stage in 3 additional instances in which premature ossification was induced by impaction with the Cotton mallet. He<sup>11</sup> now employs impaction in all cases except when there is acute slipping, believing probably correctly, that union of the epiphysis to the femoral neck by whatever means is the primary consideration.

Perkins<sup>12</sup> reported a case of surgical realinement by the Wilson method which resulted in aseptic necrosis of the femoral neck.

Ferguson and Howorth<sup>13</sup> studied 70 cases. Improvement was noted in 3 cases of slight slipping in which no treatment was given and in 12 cases of slight slipping in which the patient was treated with braces. Traction was used in 9 cases; 7 were too recent to enable one to determine the end-results, but in 2 cases in which the patient was treated several years previously the results were good. Although manipulation was employed in 21 cases, it failed to realine the head in 18. In the 3 cases in which it was successful the displacement was slight, and the reduction was accomplished within one month after the onset of the disease. Operation was performed in 18 cases. In 11 cases attempts to realine the head were made—in 5 by freeing the head at the epiphyseal line and in 6 by cuneiform osteotomy of the epiphyseal line. Of the cases followed up, in 3 there was anatomic but no functional improvement, and in 3 the condition was much worse. In all of the patients the condition was one of long standing, and several patients previously had had manipulations. A reconstruction operation was performed in 2 cases—in one after four attempts at reduction and one operation and in the other after an attempt to hold the head by a spike which penetrated the joint. No results are given. Secondary subtrochanteric osteotomy for a stiff hip or a contracture was performed in 4 cases. In 1 case in which drilling had been done, a good result was reported, with ossification at the epiphyseal line after three months. Ferguson and Howorth concluded that adequate rest for the hip is the most important factor in obtaining a good result, particularly in cases of slight slipping. They stated that if the period before expected union is longer than six months drilling across the epiphyseal line will hasten union. In recent cases in which marked slipping has occurred manipulative reduction is recommended. In cases of chronic marked slipping surgical reduction or subtrochanteric osteotomy, after quiescence, is advised.

---

11. Jahss, S. A.: Personal communication to the authors.

12. Perkins, G.: Treatment of Adolescent Coxa Vara, *Brit. M. J.* 1:55 (Jan.) 1932.

13. Ferguson, A. B., and Howorth, M. B.: Slipping of the Upper Femoral Epiphysis: A Study of Seventy Cases, *J. A. M. A.* 97:1867 (Dec. 19) 1931.

Taylor<sup>14</sup> reported 23 cases with the follow-up histories for 13 hips. Manipulation was used in 4 instances, with good results in 1, poor results in 2 and fibrous ankylosis in 1. In 1 case of surgical realinement function was good, but marked arthritic changes appeared. Transtrochanteric osteotomy was used in 6 cases of gradual slipping, with good results in 3 cases, fair results in 2 cases and bad results in a case in which reslipping occurred owing to too short a period of immobilization and in which a bifurcation operation was ultimately required. In 1 case the hip was immobilized for eighteen months with a good functional result but only fair anatomic alinement. Another patient under treatment for five weeks by gradual traction had good anatomic alinement with promising function.

TABLE 1.—Summary of the End-Results in 147 Cases Reported to Date

	Number	End-Results			
		Good	Fair	Poor	Bad
Nonoperative procedures					
No treatment.....	6	4	2	0	0
Cast.....	10	10	0	0	0
Brace.....	14	12	2	0	0
Traction.....	8	8	0	0	0
Cotton mallet.....	3	3	0	0	0
Manipulation.....	9 acute 58 chronic	6 15	3 18	0 9	0 16
Total.....	105	55	25	9	16
Operations					
Slipping.....	24	11	5	1	7
Osteotomy for coxa vara.....	3 1 11	0 1 7	1 0 2	0 0 0	2 0 2
Total.....	39	19	8	1	11

Taylor concluded that patients with this condition should be treated by manipulation and prolonged protection from weight bearing, the manipulation being best accomplished by prolonged extension of the limb on a frame.

Wardle<sup>15</sup> discussed treatment by gradual traction as opposed to rapid traction and reported good end-results in the cases of 3 patients treated by this method. Two were cases of acute traumatic slipping of one month's duration, and in the third the slipping was nontraumatic and of eight weeks' duration. Wardle treated his patients by traction in a frame and bandaging in internal rotation, the opposite leg being used for countertraction. It took from eight weeks to three months to accomplish the reduction, after which braces were applied for a

14. Taylor, V. J. M.: Displacement of the Upper Femoral Epiphysis, Brit. M. J. **11**:1003 (Dec.) 1932.

15. Wardle, E. N.: Etiology and Treatment of Slipped Epiphysis of the Head of the Femur, Brit. J. Surg. **21**:313 (Oct.) 1933.



period of about one year. His complications included pressure sores and foot drop, but his good end-results appeared to him to justify the difficulties encountered. He concluded that gradual traction was the most efficient form of treatment and that subtrochanteric osteotomy was an excellent second line of defense after the deformity had consolidated. He condemned surgical operation (table 1).

#### COMMENT

In the foregoing summary we have collected cases from the literature which were followed up and in which the results were accepted as end-results by the authors, and we have attempted to classify the results according to the procedures employed. Within certain limits this is impossible, since in many instances these divisions were not clearly stated in the text. The classification, such as it is, gives the results and the conclusions which have served to crystallize surgical opinion regarding what can be accomplished in this disease. There has been built up, as a result, an erroneous impression which is unjustified by the facts, because the situation is worse than could be expressed by figures. We do not imply that the disease is uniformly mistreated, but it is our feeling that the value of radical surgical measures has been unfortunately and unnecessarily overemphasized.

Our summary reveals a somewhat surprising picture. According to the testimony of the various authors, good results were obtained in approximately 50 per cent of all of the cases, regardless of whether radical or conservative procedures were employed. Were we to accept these figures as an accurate portrayal of the situation, we should be unduly optimistic regarding the treatment of the disease. Our experience is in no way comparable, and when we study the cases reported the reasons for this discrepancy become obvious.

In some of the cases in which the results were reported as end-results, the period of observation after treatment was too short to permit of a positive estimate of the success of the treatment. In some instances the position of the alleged replaced femoral head was misinterpreted from the roentgenogram; we have found this to be a common source of error. The osteoporosis of the epiphysis following immobilization makes visualization of the presenting cartilaginous plate surface of the head extremely difficult, particularly through a plaster cast.

Many of the patients who were successfully treated by means of braces or casts had had one or more manipulations. Their cases should have been classified as instances of failure following manipulations.

Some of the good end-results following correction by surgical intervention were in early cases. One would now hardly recommend this procedure.

In the 58 chronic cases in which manipulation was done, there were 15 successful repositions of the femoral head. This is a curious fact when one considers how difficult it is at times to replace the epiphysis even by operation or in acute traumatic cases.

How are we to classify the cases of over 20 per cent of the patients who were treated and for whom no adequate follow-up data exist?

#### SOURCE OF MATERIAL AND DEFINITION OF TERMS

All of the patients in our own series were treated by the orthopedic departments of the Hospital for Joint Diseases, and the majority were semiprivate patients and patients from the wards. This is fortunate, because their records are complete and the results more closely represent individualistic and unrestricted efforts. We are therefore enabled to present an accurate cross-section of the end-results of all of the accepted methods of treatment. Many of the patients were observed over a period of years.

We have rejected cases the records of which are incomplete or unsatisfactory or in which the films showing the original condition and end-result are not available.

The results were designated as good, fair, poor or bad, depending on the degree of anatomic restitution. In the determination of the functional end-results, we eliminated subjective impressions and accepted verbatim the clinician's appraisal or interpreted, in unequivocal terms, his analysis of what had been accomplished. We were aware, of course, that one had to consider end-results in terms of the original condition, and we took cognizance of the fact that imperfect anatomic restitution was in no way incompatible with good function.

Medical language does not lend itself readily to an extremely fine description of minute pathologic alterations. Attempts at classification in most instances resemble a melodic episode in which the theme of the subject is suspended or perhaps even lost in the by-paths of the accompanying instruments. It seemed futile to divide the lesion into innumerable types all predicated on the degree of slipping of the femoral epiphysis. Numerous imponderable factors militate against such fine distinctions, and for purposes of study we simply divided the lesions into the following types:

Slight slipping

Marked slipping:

(a) Acute traumatic

(b) Chronic

Union in malposition

Old cases

*Slight Slipping.*—This group includes cases in which there is little or no slipping. In some of the cases the roentgenogram shows a normal picture but clinical signs and symptoms are suggestive. The roentgenogram usually shows a widening of the epiphyseal line which is best demonstrated when the hip is examined with the femur in external rotation. Occasionally there is a distinct resorption on the metaphyseal side of the epiphyseal line, with a moderate increase in the density of the articular cortex of the epiphysis subjacent to the epiphyseal cartilage plate. Loss of the "hump" formed by the superior quadrant of the epiphysis at the epiphyseal line sometimes occurs.

*Marked Slipping.*—The roentgenograms in this group show a typical picture. The degree of slipping of the capital epiphysis depends on the severity of the lesion and at times may amount to as much as 1 inch (2.5 cm.). As the femoral epiphysis slips, it rotates downward, backward and inward, so that a variable extent of its epiphyseal plate surface faces forward. As a result of this rotation, there is an apparent flattening of the head. The hump previously referred to disappears, and a distinct gap is noted between the epiphysis and the neck of the femur at the upper end of the epiphyseal line. The neck of the femur is displaced anterior to the epiphysis. Distinct resorptive changes occur in the neck, so that even the apparently flattened femoral head appears too large for it.

Clinically, these cases may be divided into the acute and the chronic type. In the acute type there is usually a history of severe trauma with associated clinical symptoms of a fracture. Our cases of acute slipping corresponded to the early cases of Badgley, the early cases with trauma of Jahss and the rapid complete cases of Perkins. In the chronic cases there may or may not be a distinct history of trauma or, at best, repeated mild injuries never sufficiently severe to incapacitate. It is difficult at times to judge whether a case belongs to the acute or the chronic type. The histories of clinical patients are notoriously unreliable, and many children suffer repeated falls without epiphyseal displacement before their final severe trauma. Wilson called these marked cases instances of complete separation and did not attempt to subdivide them. Ferguson and Howorth referred to them as cases with slipping. Our chronic cases corresponded to the advanced cases of Badgley, the late case of Jahss and the repeated incomplete cases of Perkins.

*Union in Malposition.*—These cases resemble those classified on roentgen examination as cases of marked slipping except that the head and neck are malunited. There is a distinct increase in the width of the femoral neck, with a fairly pronounced coxa vara deformity. The femoral head is frequently flattened and somewhat deformed. They correspond to the healed cases of Badgley or the residual cases of Ferguson and Howorth.

*Old Cases.*—This group represents the end-results of all types of cases. After the age of 18 years secondary arthritic changes were practically universal in our cases as well as in those reported by previous writers.

#### ANALYSIS OF CASES

We were able to review the roentgenograms of 101 patients with a condition diagnosed as slipping of the upper femoral epiphysis who were observed from 1925 to 1933 and who were treated by 114 procedures. Of these patients, 14, 8 of whom were adults, had bilateral slipping. A total of 107 hips were studied in children. The youngest patient was aged 8 years, and the oldest was a girl of 18. Forty children were extremely obese and of the Fröhlich type; 51 had a distinct history of trauma. According to the classification as given, there were 54 patients with slight slipping and 53 with marked slipping, the degree varying from little or no displacement to almost complete rotation of the capital epiphysis so that the plate surface faced forward.

Eleven patients received no treatment, as they did not return to the outpatient department. Eight received nonorthopedic treatment such as ultraviolet irradiation with the air-cooled quartz mercury vapor

arc lamp or endocrine therapy. In our series, therefore, 88 hips of children were treated by 114 procedures. In 29 instances operation was performed, and in 85, nonsurgical procedures were employed. More than 1 procedure was employed for 18 of the 88 hips, and in 1 instance 6 different methods of correction were employed.

#### CASES IN WHICH CONSERVATIVE TREATMENT WAS EMPLOYED

All the patients who were observed prior to 1926 were treated conservatively. This method was also employed when permission for surgical intervention was refused, or when the patient's physical condition did not warrant radical measures. The cases in which conservative treatment was given were distributed as follows:

	No. of Cases
Manipulation .....	58
Immobilization in a cast.....	9
Impaction by the cotton mallet.....	9
Immobilization in a cast and traction.....	5
Traction .....	1
Rest (opposite hip).....	3

*Manipulation*—According to the classification as given, there were 21 cases of slight slipping and 23 cases of marked slipping, making a total of 44, in which the patients underwent 58 manipulations. Only 35 cases were followed up for function. The method of manipulative reduction varied only slightly in the different services. The Jahss method was employed in 3 cases, and the Leadbetter method in 1. The Whitman abduction method was employed in the remaining cases.

A distinct history of trauma was obtained for 19 of the patients with marked slipping, and only 5 showed immediate improvement in alignment after manipulation, but these 5 were treated within three months after the trauma. In 11 cases manipulation was resorted to more than once, as the head was not realigned at the first effort; in 1 case manipulation was performed 5 times. In 7 cases in which manipulation was unsuccessful operation was subsequently performed. In 2 cases manipulation followed operation. One of our patients required a secondary operation for knock-knee several years after the occurrence of epiphyseal union at the hip. In 1 case aseptic necrosis of the femoral head developed following manipulation, and in a case in which operation was performed a similar complication developed after manipulation at another hospital.

In the cases of slight slipping, there were good functional results in 13 instances, fair results in 2 and poor results in 3. It is notable that in these cases of slight slipping there were no bad functional results. In the cases of marked slipping, however, there were good results in only 5 instances, fair results in 4, poor results in 5 and bad results in 3.

*Immobilization in a Plaster Cast.*—Nine patients were treated by immobilization of the limb in a spica cast. There was slight slipping in 4 cases and marked slipping in 5. All were followed up. In 2 cases of slight slipping good results were obtained, and in 2, fair results. The 5 patients with marked slipping had poor results because of marked limitation of motion at the hip due to extreme malalignment of the capital epiphysis.

*Impaction by the Cotton Mallet.*—Impaction by means of the Cotton mallet to promote union was used in 9 cases. In 6 there was slight slipping, and in 3, marked slipping. Orthopedic treatment had not previously been used in these cases. The shortest period within which

TABLE 2.—Results in Eighty-Five Cases in Which Conservative Procedures Other Than Operation Were Employed

Treatment	Manipulation		Spica Cast		Cotton Mallet		Cast and Traction		Traction		Rest		Total	
No. of patients examined....	58 (42 cases)		9		9		5		1		3 (opposite sides)		85	
Degree of slipping*.....	S	M	S	M	S	M	S	M	S	M	S	M	S	M
	23 (19 cases)	35 (23 cases)	4	5	6	3	3	2	1	0	3	0	40	45
Anatomic results														
Good.....	13	5	2	0	5	2	1	0	1	0	3	0	25	7
Fair.....	7	7	2	0	0	0	0	0	0	0	0	0	9	7
Poor.....	3	17	0	5	1	0	2	2	0	0	0	0	6	24
Bad.....	0	6	0	0	0	1	0	0	0	0	0	0	0	7
Functional results														
Good.....	13	5	2	0	5	2	1	0	1	0	3	0	25	7
Fair.....	2	4	2	0	0	1	1	0	0	0	0	0	5	5
Poor.....	3	5	0	5	1	0	0	2	0	0	0	0	4	12
Bad.....	0	3	0	0	0	0	0	0	0	0	0	0	0	3
Repeated surgical procedures	1	0	0	0	0	0	1	0	0	0	0	0	2	6
Repeated nonsurgical procedures.....	4	12	0	0	0	0	0	0	0	0	0	0	4	12

\* S indicates slight, and M, marked.

union occurred was two months after impaction, in a patient aged 14. and the longest period was over twelve months, in a patient aged 10 years.

In 7 cases the results were good and the function was excellent. The only residual symptoms were slight limitation of internal rotation and slight shortening of the limb, such as are nearly always found in treated and untreated patients with epiphysiolysis. The other 2 patients had poor results. One patient, aged 10 years, fell (one year post-operatively) and sustained a fracture of the neck of the femur on the involved side after what appeared to be an excellent result. He has now a few degrees of motion in the hip joint. This case should rightfully be considered an instance of an excellent result following impaction, but it was unfortunately complicated by the accident. The second patient.

aged 14, with marked slipping sustained an almost complete separation of the capital epiphysis after impaction. The epiphysis united in malposition, and the patient now has fair function.

*Immobilization in a Cast and Traction.*—The method was employed in 5 instances. The patient was treated by skin traction until all of the muscle spasm was overcome; the limb was then immobilized in a plaster spica. Three of these patients had slight slipping, and 2, marked slipping. In 1 of the cases of slight slipping the result was good, and in 2 the function was poor. Operation was subsequently performed in 1 of these 2 cases. The 2 patients with marked slipping showed poor function. The head of the femur was not realigned by our method of skin traction.

*Traction.*—In only 1 case of slight slipping in which traction was employed was there a good result.

*Rest.*—There were 3 cases of bilateral slipping in which only one side was actively treated. All were cases of slight slipping; good results were obtained on the untreated side after the patient was given prolonged rest in bed (table 2).

#### CASES IN WHICH OPERATION WAS PERFORMED

All except 2 of the cases in which operation was performed were instances of marked slipping of long duration. In some cases previous conservative measures had failed. In these instances the deformities were pronounced, and pain and disability were prominent features of the process. Operation by drilling, however, was performed in only 6 cases of slight slipping. The methods employed were as follows:

	No. of Cases
Reconstruction operation.....	11
Realignment of the epiphysis.....	5
Pegging .....	5
Drilling operation .....	6
Osteotomy for coxa vara.....	2

*Reconstruction Operation.*—A reconstruction operation or arthroplasty was performed on 11 patients with marked slipping of more than six months' duration. In 3 of the patients previous manipulation had failed, and in 2 previous realignment of the head was unsuccessful. In 1 the deformity had increased despite the treatment with traction.

In all of these cases functional and anatomic end-results were poor. In 3 cases a limited degree of motion but no rotation was retained; in 1 case there was passive but no active motion. There was marked osteoarthritis in 2 patients and complete bony ankylosis of the hip joint in 4. One patient showed aseptic necrosis of the femoral epiphysis; when the patient was last seen the epiphysis appeared to be ankylosing.

A secondary operation was required in 2 cases. One patient, in whom ankylosis in poor position had occurred, required a subtrochanteric osteotomy. Another patient had marked shortening, so that a lengthening of the tibia was undertaken; nonunion resulted. Two years later, however, following bone graft operation, osteomyelitis developed. One patient sustained a fracture of the shaft of the femur during operation and now has a residual stiffness of the knee following pin traction.

*Realinement of the Epiphysis.*—This procedure was employed in 5 cases, in 2 of which previous manipulations had failed. Realinement was not simple, since the femoral head was often found either partially or completely united to the shaft. Callus was often found about the neck of the femur, according to Ferguson and Howorth. At best, how-

TABLE 3.—Results in Twenty-Nine Cases in Which Operation Was Performed

Treatment	Recon- struc- tion		Realine- ment of Head		Wedge and Peg		Drilling		Osteotomy for Coxa Vara		Total	
No. of patients examined.....	11		5		5		6		2		29	
Degree of slipping*.....	S	M	S	M	S	M	S	M	S	M	S	M
Anatomic results	1	10	0	5	1	4	6	0	0	2	8	21
Good.....	0	0	0	0	1	0	6	0	0	1	7	1
Fair.....	0	0	0	1	0	2	0	0	0	0	0	3
Poor.....	0	2	0	0	0	1	0	0	0	0	0	3
Bad.....	1	8	0	4	0	1	0	0	0	1	1	14
Functional results												
Good.....	0	0	0	0	1	0	5	0	0	1	6	1
Fair.....	0	0	0	1	0	0	0	0	0	0	0	1
Poor.....	1	2	0	0	0	1	0	0	0	0	1	3
Bad.....	0	8	0	2	0	1	0	0	0	1	0	12
Reoperations												
Operation.....	0	0	0	2	0	0	0	0	0	0	0	2
Still under treatment.....	0	0	0	0	0	2	1	0	0	0	1	2

\* S indicates slight, and M, marked.

ever, the so-called realinement of the epiphysis was only partially successful; a residual displacement was present in all of our cases. In 4 of our cases there was a distinct history of trauma; all of the patients were seen more than eight months after the onset of symptoms. There was a fair functional and anatomic result in 1 case. Bad results were obtained in 4 cases of surgical realinement of the head. In 2 of these cases there was complete ankylosis postoperatively, and in 2 others the patient was subjected to reconstruction operation at a later date—in 1 because of nonunion of the head six months after surgical realinement and in the other because of malunion.

*Pegging.*—In this series, 5 patients were treated by resection at the epiphyseal line, realinement of the head with the neck and fixation with an ivory screw or bone peg. With 1 exception, these were marked cases. Two were traumatic and of eight months' duration, and 2 were nontraumatic. In 2 cases the patient required subsequent manipulation

for flexion contractures; in 1 of these cases drilling was subsequently resorted to at another hospital to promote union. In both cases the functional results were poor. Two patients are still under observation. The only good result was in 1 patient with slight slipping who had been observed for five years.

*Drilling.*—Simple drilling was employed in 5 cases, and in an additional case a peg was inserted through the drill hole. In 1 case of bilateral slipping the opposite side, on being manipulated, united within five months; the drilled side, after eight months. In a second case of bilateral slipping the side for which rest only was employed united before the drilled side. In this instance union was demonstrated eight months after operation. Although the patients in 2 other cases were only 10 and 11 years old, respectively, union was effected after three months. There were no complications in this group, and the functional results were uniformly good.

*Osteotomy.*—Two untreated patients were seen in this institution after union had occurred with residual coxa vara deformities. In 1 case a wedge osteotomy through the neck of the femur was performed; it did not correct the deformity. In the second case a subtrochanteric osteotomy through the shaft of the femur produced an excellent result (table 3).

#### COMPLICATIONS AND SEQUELAE

There were 9 cases with complications in the 29 cases in which operation was performed, and 4 cases with complications in the 85 cases in which operation was not performed. In 1 case in which operation was performed and in 1 case in which manipulation was employed fractures were sustained on the operating table. Secondary arthritis followed in 3 cases in which operation was performed and in 1 case in which manipulation was employed. Of 5 cases of aseptic necrosis operation was resorted to in 4 and manipulation in 1. In 1 of these cases and in 5 cases in which operation was performed complete ankylosis of the hip subsequently developed.

Manipulation was performed on 4 patients prior to operation and on 2 patients after operation. Two patients underwent resection of the epiphyseal line prior to a reconstruction operation. Secondary operations were required in 3 cases: a lengthening of the bone of the tibia, a subtrochanteric osteotomy of the femur and a wedge osteotomy of the tibia.

#### COMMENT

In judging the results obtained in cases in which the patients were treated by operations and by conservative methods, it is best to compare the cases of slight and those of marked slipping of the epiphysis separately.



The principles applied in the treatment of preslipping or slight slipping are fairly well defined. The desire is to prevent further slipping; in order to do so one attempts to hasten the ossification at the epiphyseal line. The common methods are the use of casts with or without traction, manipulation, drilling and impaction with the Cotton mallet.

In our series, the group in which manipulation was employed was by far the largest, and the cases of marked or chronic slipping predominated. Satisfactory reposition was accomplished in more than 50 per cent of the cases of slight slipping, and there were no bad results. One is led to suspect that these patients would have done as well with immobilization in casts. Rest alone in many instances will accomplish more than repeated attempts at correction. In many of the cases of bilateral slipping the untreated side healed as well as the treated side, particularly when inactivity was accomplished by rest in bed or by a plaster cast. Of the cases of marked slipping, realinement in good position occurred in only 5, and it is important to emphasize that all of these were cases of acute slipping. In the cases of chronic slipping the condition was unaffected except in a few instances in which it was made worse. This leads to a consideration of the results of the unsuccessful manipulations. The procedure was repeated in many of our cases and followed by some radical methods, which also resulted in failure. Operation followed manipulation in 6 cases. It therefore seems obvious that it is extremely inadvisable to attempt repeated traumatization of the hip by manipulative correction. In this respect our experience is in conformity with that reported in the literature. In 6 of the 9 cases of acute slipping in the series of cases previously reported, the epiphysis was well alined, but of the 58 cases of chronic slipping in which manipulation was employed satisfactory results followed in only 15; in the remainder the results were fair, poor or bad. (It is important to remember that the chronic cases reported in previous publications are not always clearly classified as showing either slight or marked slipping.)

Of the 3 cases of slight slipping in which a cast in gradual traction was employed, in only 1 was a good result obtained. Whether or not these results could have been further improved by Wardell's method of gradual traction is an open question; this method has not been employed at the Hospital for Joint Diseases. It is obvious from our experience that gradual traction would be worthless in the cases of marked chronic slipping, especially if one bears in mind the nature of the process. In many instances the epiphysis is rotated downward, backward and inward. The application of traction to pull down the femoral neck and thus correct the rotary displacement of the epiphysis is an ameliorative gesture usually futile except in cases of acute slipping.

One of the advantages claimed for the drill method is that it hastens union of the epiphysis to the neck of the femur. It has therefore been

recommended in cases in which the period of expected union is greater than six months. That this method is effective was demonstrated in patients, aged 10 and 11 years, in whom premature ossification through the epiphyseal line occurred three months after drilling. This method was employed only in cases of slight slipping. One must remember that this is a fairly new procedure and that it entails all the dangers of an operation. It is, furthermore, difficult at times to estimate preoperatively the amount of anterior displacement of the neck of the femur, and the drill holes are not always placed in a technically correct position. The danger of perforating the femoral epiphysis and entering the hip joint proper is not a remote possibility; fortunately, it did not occur in any of our cases. There were no complications in this group.

Impaction with the Cotton mallet as advocated by Jahss to hasten ossification through the epiphyseal line was successful in 7 of the 9 patients treated in this manner. This objective was accomplished within two months in a child aged 14, and delayed for twelve months in another child aged 10 years. These results, however, represent the extremes; the average union was achieved in from four to six months. Of the 2 cases in which fair results were achieved following this treatment, in only 1 was the result directly attributable to the impaction, and in this instance the femoral epiphysis was further displaced following treatment. In the second case the patient fell on the affected hip and sustained a fracture of the neck of the femur after what appeared to be a successful result. Union of the capital epiphysis to the femoral neck must have occurred, since it is reasonable to believe from our experience that if that were not the case the epiphysis would again have been displaced. It is also uncommon to see a fracture of the neck of the femur in a child. Of the 9 patients treated, 7 obtained excellent functional restorations of the hip, and when one considers that there were 3 cases of marked slipping in the group these results are extremely gratifying. The advantage of the method is that it is a nonoperative procedure which produces premature ossification quickly and which, as a result, reduces substantially the period of disability. The patients were observed until fusion occurred at the epiphyseal line, but it remains to be seen whether or not unusual arthritic changes develop because of the maneuver.

In the group in which operation was performed and which comprised most of the cases of marked slipping correction was attempted by reconstruction, realinement of the epiphysis, wedge resection to correct the coxa vera deformity or manipulation.

Reconstruction operations were performed on 11 patients. In 3 previous manipulations had been unsuccessful, and in 2 previous attempts to realine the head had failed. In 1 the deformity had increased despite the treatment with traction. In the patients operated on the result was poor, and in the single instance in which operation was performed in an

early case the result was bad. One questions the wisdom of employing so radical a procedure for the correction of so simple a deformity. From our study it is apparent that there is no justification for the operation in this disease, and our conclusion is borne out by the cases previously reported. Of the 3 cases on record, the results were fair in 1 and bad in 2. In other words, of a total of 14 cases, the results were bad in 9 and fair or poor in 5.

Surgical realinement of the epiphysis was often unsuccessful because of the difficulty of freeing it from adhesions or callus. It is obvious that if the head is not realined the purpose of the operation is defeated. Examination of the roentgenograms in many instances proved that the position of the epiphysis was uncorrected by this maneuver. Of the

TABLE 4.—Cases in Which Operation Was Performed Compared with Those in Which Conservative Methods Were Used

Type of slipping.....	Slight		Marked		All Cases	
	No Oper- ation	Opera- tion	No Oper- ation	Opera- tion	No Oper- ation	Opera- tion
Treatment.....						
Number of cases.....	40	8	45	21	85	29
Anatomic results						
Good.....	25	7	7	1	32	8
Fair.....	9	0	7	3	16	3
Poor.....	6	0	24	3	30	3
Bad.....	0	1	7	14	7	15
Functional results						
Good.....	25	6	7	1	32	7
Fair.....	5	0	5	1	10	1
Poor.....	4	1	12	3	16	4
Bad.....	0	0	3	12	3	12
Reoperation						
Surgical procedures.....	2	0	6	2	8	2
Repeated nonsurgical procedures..	4	0	12	0	16	0
Still under treatment.....	0	1	0	2	0	3

23 cases reported in the literature, there were good results in only 11 cases and fair, poor or bad results in 12. Of the 5 patients treated in this institution, 4 had bad results and only 1 fair results. The condition was usually made worse, and at the best there was obtained only a fair anatomic reposition of the head without functional improvement.

Wedge resection was unsuccessful in 2 cases of marked slipping, and the only good result was in an early case. Again we question the advisability of employing so radical a method in an early lesion.

Only 5 of our patients were successfully treated by manipulation, and, as we have already indicated, in none of the chronic cases was realinement produced (table 4).

The solution of the problem obviously must depend on an intelligent appraisal of the following questions:

1. What is the degree of slipping of the femoral head, and what chances for success do conservative methods offer? Conversely.

if such methods are unsuccessful, what would be the indication for surgical correction, and what would be the method?

2. It seems axiomatic that the management of acute slipping and that of chronic slipping imply wholly different principles or concepts. In the first, there is an intra-articular fracture with displacement of fragments; in the second, associated with the original catastrophe, there are secondary atrophy, resorption of localized areas of bone and perhaps fibrous or early bony malunion. In what manner do these secondary changes in the femoral head and neck militate against manipulative correction? Has one neglected the significance or importance of these secondary changes in the surgical corrections?

3. What would be the management of a chronic case in which the epiphysis has spontaneously united in fair position but in which pain and moderate disability are the dominant symptoms?

#### CONCLUSIONS

On the basis of the end-results reported here, the following conclusions appear to be justified:

1. Very early cases in most instances heal best by immobilization or rest without manipulation. Repeated efforts to reduce the deformity, as evidenced by a multiplicity of corrective maneuvers, appear to aggravate the situation. Judging from comparable cases on record, one cannot escape the impression that in many instances the end-results would have been better had the patients been left entirely alone.

2. In a few cases of bilateral slipping the untreated side healed as well as the treated side, or the side treated conservatively healed as well as the side treated radically.

3. In the cases in which manipulation and operation were employed the end-result was only too frequently worse than the original deformity.

4. In many cases manipulation failed to realine the femoral head and aggravated the deformity. Manipulation appears to be unwarranted in case of slight slipping, ineffectual in cases of marked, chronic slipping and definitely indicated in cases of acute traumatic slipping. It is possible to have a stiff joint even in a case in which manipulation has been employed.

5. In the early and moderately advanced cases impaction by the Cotton mallet appears to be a safe nonoperative method to hasten ossification through the epiphyseal line and to arrest the deformity. The functional results are usually good. This method appears to be contraindicated, however, in the acute traumatic cases with displacement of the epiphysis.

6. Operation by drilling was employed in cases of slight slipping with good functional results and the production of premature ossification through the epiphyseal line.

7. In cases of chronic marked slipping the subtrochanteric osteotomy represents the totality of effective and permissible procedures to correct the deformity.

8. In cases of so-called realinement of the epiphysis by operation, the position of the allegedly realined head often remained exactly as it was before operation.

9. Even if anatomic restitution is satisfactory, complete redislocation of the epiphysis may occur if the period of immobilization is short.

10. Reconstruction operations may result in infection, necrosis of the remaining head and fixation of the joint. These appear to be the least desirable of all procedures. We can postulate categorically that the more radical the surgical procedure the worse the end-results.

11. In many of the cases of so-called good end-results, there are extensive changes in the contour of the femoral head and joint within five years.

Dr. Herman Frauenthal, Dr. Harry Finkelstein, Dr. Samuel Kleinberg and Dr. Leo Mayer permitted us to study cases from their services.

# RATE OF ABSORPTION OF ALVEOLAR GASES IN RELATION TO HYPERVENTILATION

K. E. LEMMER, M.D.

AND

E. A. ROVENSTINE, M.D.

MADISON, WIS.

During experimental work in the production and surgical application of closed endobronchial anesthesia the behavior of certain anesthetic gases in the obstructed lung was noted. The ease with which complete bronchial obstruction could be obtained and the speed of absorption of gases from the obstructed lung led us to repeat, by this technic experimental work reported by Coryllos and Birnbaum.<sup>1</sup>

The importance of atelectasis in the production of postoperative pneumonia, the different opinions expressed as to the etiology of such atelectasis and the varied ideas as to the treatment make the subject important. It is of special interest to the surgical team charged with the responsibility of minimizing any causative factors as well as of instituting immediate and efficient therapeutic measures. Our practice had been to hyperventilate certain patients during recovery from the effects of anesthesia, particularly after anesthetization with ether. Such hyperventilation was commonly done by giving mixtures of oxygen and carbon dioxide. To prove or disprove the error of such a procedure or to determine the advisability of using carbon dioxide and air rather than oxygen was the immediate purpose of the study.

The absorption of gases from the lung was observed as early as 1879;<sup>2</sup> however, it was not until the exhaustive experimental studies by Coryllos and Birnbaum in 1932<sup>1</sup> that definite and conclusive evidence was obtained that the absorption of gas from the obstructed lung is dependent on several factors: first, the speed of diffusion of the particular gas through space; second, the partial pressure of the gas; third, the solubility of the gas; fourth, the integrity of the epithelium, and, fifth, the pulmonary circulation. The nature of a gas helps to determine its solubility, the more basic or acid gas being more soluble than the neutral gases.

---

From the departments of surgery and anesthesia, University of Wisconsin Medical School, and the Wisconsin General Hospital.

1. Coryllos, P. N., and Birnbaum, G. L.: *Am. J. M. Sc.* **183**:317 (March) 1932.

2. Lichtheim, L.: *Arch. f. exper. Path. u. Pharmacol.* **10**:54, 1878.

In these experiments, large full-grown dogs were used in order that the work might be simplified by having available a large trachea and larger upper air passages. Each dog was given morphine and atropine before being subjected to anesthesia, which was induced with ether by the open drop method. When anesthesia had reached a plane sufficiently deep to give complete abduction of the cords and easy intubation of the trachea, the mask was removed and the glottis was exposed by extending the tongue and lifting the epiglottis with a sponge forceps. Two endobronchial airways of woven silk fabric, each with an inflatable cuff, were placed in the trachea. The airways were about 18 inches (45.7 cm.) in length. The inflatable cuffs were of the Guedel-Waters<sup>3</sup> type and were placed within 1 inch (2.5 cm.) of the end of the airway. The terminal inch of the catheter was molded in warm water so that it curved slightly toward the side of the beveled tip, and petrolatum was applied for lubrication. No. 20 F catheters were found to be a proper size for the large dogs used. With the catheters in the trachea, one and then the other was placed with its terminal end in the main bronchus on either side. This was accomplished by pushing the airway close to the right side of the glottis with the curved tip pointing to the left and sliding the tip down the left tracheal wall to enter the left bronchus, and vice versa. The first feeling of resistance suggested the entrance into the bronchus, and later resistance to advance indicated that the catheter had entered too far. With both endobronchial airways in place one was quickly attached to the anesthetic apparatus, which consisted of a canister containing soda lime to absorb carbon dioxide and a spirometer. The system was immediately filled with an anesthetic mixture of ether and oxygen, and a constant flow of oxygen was maintained to supply the metabolic requirements of the dog. The cuff on each catheter was inflated. There was then produced a respiratory system of one lung and the anesthetic apparatus. The other lung was closed except for the endobronchial airway.

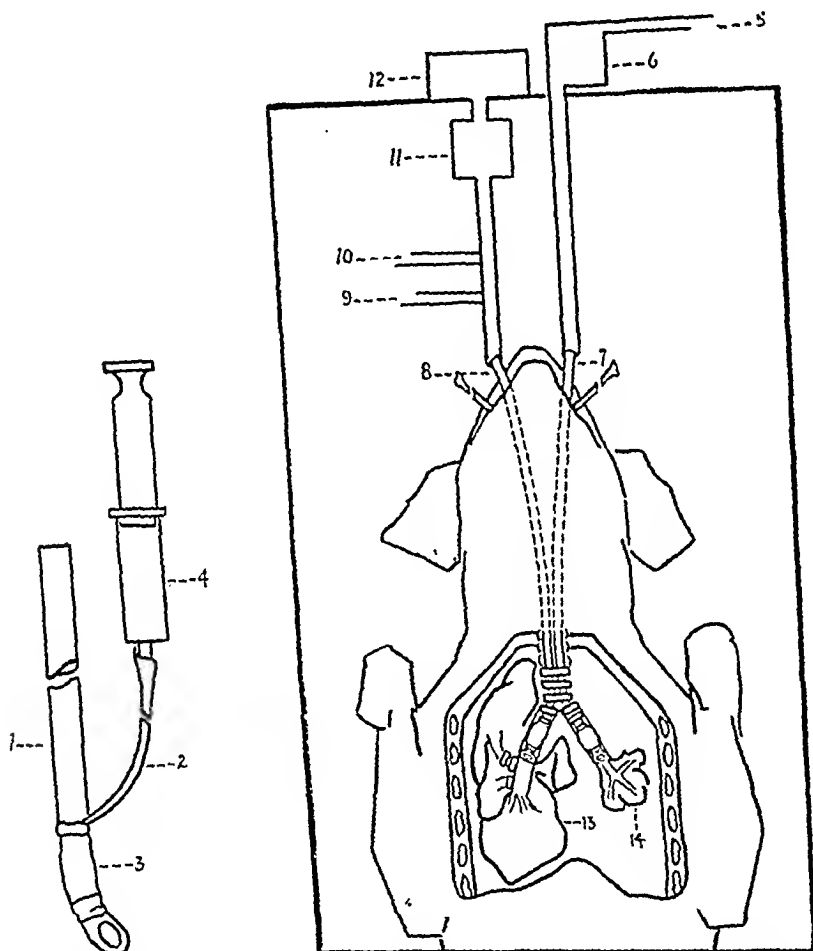
Artificial respiration, using a spirometer for inflation and deflation, was instituted in one lung, and the other was permitted to collapse. A water manometer was incorporated with the closed system to assure uniform intrapulmonic pressure. The wall of the chest was then carefully removed so that circulation to the lung was unimpaired and both lungs were brought into direct view. The figure diagrammatically represents the experiment.

Control was complete in the one lung when the inflatable cuff was distended. Measured amounts of the experimental gases were introduced through the endobronchial catheter into the experimental lung

---

3. Guedel, A. E., and Waters, R. M.: *Ann. Otol., Rhin. & Laryng.* 40:1139 (Dec.) 1931.

by way of an accurate flow meter. The same amount of gas (600 cc.) was used each time, and the endobronchial catheter was clamped to prevent escape. The rate of absorption was then determined. Owing to the extended time needed for some gases to absorb completely or for the lung to become entirely atelectatic, it was necessary to select a condition of the lung constant for all gases and beyond which absorp-



A diagrammatic sketch of the experimental apparatus, showing: 1, the endotracheal catheter; 2, inflating catheter to the inflatable cuff; 3, inflatable cuff; 4, syringe; 5, gas inlet; 6, flow meter; 7, catheter to the deflated lung; 8, catheter to the respiring lung; 9, source of the supply of anesthetic; 10, water manometer; 11, carbon dioxide absorber; 12, spirometer; 13, respiring lung, and 14, experimental lung.

tion was not determined. When the lung was about one-eighth its normal size there appeared dark red or black patches over the entire surface, and it was to this point that the absorption rates of the different



gases were compared. In each case the lung gradually decreased in size without any obvious alteration of shape, appearance or color until it was about one-sixth its normal size. It was found that the first rate of absorption of gas introduced into a lung was less than the rate after succeeding inflations. Alveolar epithelial damage from the gases probably alters the rate of absorption. Results comparable with those already reported were obtained. Oxygen and carbon dioxide were absorbed rapidly as compared with the more inert gases, nitrogen, hydrogen, argon and helium. The anesthetic gases, nitrous oxide and ethylene, were absorbed rapidly. The table summarizes the experimental work and the average results.

*Rates of Absorption of Various Gases in the Lungs of Dogs*

Gas Used	Number of Experiments	Average Time of Absorption to Given Point
Carbon dioxide.....	9	1 min. 6 sec.
Oxygen.....	12	1 min. 20 sec.
Nitrous oxide.....	6	1 min. 42 sec.
Ethylene.....	8	2 min. 2 sec.
Hydrogen.....	3	16 min. 22 sec.
Argon.....	3	16 min. 4 sec.
Helium.....	1	18 min. 16 sec.
Air.....	12	9 min. 21 sec.
Nitrogen.....	6	12 min. 6 sec.

#### SUMMARY

The results of experiments are presented to show the comparative rates of absorption of different gases from the completely obstructed lung.

The normal physiologic processes were disturbed by opening the chest; however, carefully controlled artificial respiration in the contralateral lung maintained a good circulatory condition.

Owing to the demonstrated rapidity of absorption of carbon dioxide and of oxygen as compared with that of nitrogen and of air, it is deemed advisable to use air as a vehicle for carbon dioxide when hyperventilating patients who are recovering from surgical anesthesia.

# POSTOPERATIVE PROGNOSIS IN CANCER OF THE BREAST

RESULTS AFTER FROM SEVEN TO TWENTY YEARS IN A SERIES OF CASES STUDIED WITH REFERENCE TO THE RAPIDITY OF PREOPERATIVE GROWTH

E. MacD. STANTON, M.D.  
SCHENECTADY, N. Y.

In the April 1928 issue of the ARCHIVES OF SURGERY<sup>1</sup> I reported the end-results recorded up to July 1927 in the cases of fifty-four patients with cancer of the breast on whom I operated at some time between July 1907 and January 1926. In this paper I wish to summarize the results obtained in this same group of patients over an additional period of six and one-half years, namely, until death or until January 1934. Although the number of patients in this series is not large, I know of no other series of equal size in which all of the patients have been traced over as long a period. For the thirteen survivors in this group, the period since operation ranges from seven years and ten months to twenty years and six months, the average postoperative period being twelve years and nine months.

Except in case 40, all of the operations were typical radical excisions. No patient in this series received preoperative roentgen ray or radium treatment. Only one patient received any considerable amount of post-operative irradiation, and no influence on the growth was apparent.

All attempts to evaluate the results of treatment of cancer of the breast must be made with a full realization of the extreme variability of the course of this disease when no treatment is received. Many years ago Gross and others clearly demonstrated that when no treatment is given the extremes of survival after the first appearance of the tumor range from eight or ten weeks in cases of fulminating, so-called inflammatory, tumors to twenty-five or more years in cases of chronic, slow-growing tumors. This variability is found in all series of cases of cancer of the breast and is well illustrated in the present series. For instance, in case 53 an operation was performed only four weeks after the tumor was first discovered, but even then extensive axillary metastases were already present. The patient died of multiple recurrences six months after operation. In case 31 an operation was performed one hundred and fifty-six months after the discovery of the tumor and the patient lived for thirty-six months thereafter.

---

1. Stanton, E. MacD.: The Postoperative Prognosis of Cancer of the Breast, Arch. Surg. 16:879 (April) 1928.

In all but four of the more advanced cases, sections of the primary tumor and of the lymph nodes were cut. In 1927, when these cases were first reported, the original slides were studied in an attempt to correlate the assumed histologic malignancy, as suggested by Broders, Greenough and others, with the actually determined results. In this small series, however, no correlation was found.

The data concerning the cases herein reported have been assembled in three tables corresponding to the classification adopted by the Departmental Committee on Cancer of the British Ministry of Health.

Table 1 contains cases in class 1 of the British classification, in which, so far as could be ascertained, the growth was confined to the breast, the axillary glands not being invaded.

TABLE 1.—*Postoperative Results in Cases in Class 1*

Case	Preoperative Time after Discovery of Tumor, Months	Postoperative Results, Time in Months	
		Dead	Living
52.....	2	..	94
46.....	$\frac{1}{4}$	..	106
48.....	1	86	...
39.....	12	96	...
30.....	$\frac{3}{4}$	..	150*
26.....	$1\frac{1}{2}$	..	186
40.....	6	72	...
24.....	1	84	...
19.....	..	192	...
18.....	..	...	210
13.....	$\frac{1}{2}$	...	240
7.....	..	180	...
10.....	..	...	246
5.....	4	19	...
11.....	3	180	...

\* Died of pneumonia at 81.

Table 2 contains cases in class 2, in which the axillary glands were already invaded but no evidence of involvement of any other contiguous or distant organ or tissue was found.

Table 3 contains cases in class 3, in which either adjacent or distant organs or tissues were involved, e. g., the pectoral muscles, the skin when ulcerated, the cervical glands, the other breast, etc.

My records show that fifteen cases belonged in class 1, cancer of the breast being present without demonstrable involvement of the axillary glands.

In general from 80 to 90 per cent of the patients in class 1 remain well for five years. In this series only two of the fifteen patients died within five years after operation, and at the end of the five year period only one of the survivors had a demonstrable recurrence. Thus, twelve (80 per cent) of the fifteen patients were alive and apparently free from recurrence at the end of the five year period.

In my first report of these cases I summarized the results in the cases belonging in class 1 by saying: "If all cancers of the breast could be operated on before glandular involvement, this disease would be largely conquered." That subsequent results have not altogether confirmed this prophecy is shown by the fact that while only two of the

TABLE 2.—*Postoperative Results in Cases in Class 2*

Case	Group A	Preoperative Time after Discovery of Tumor, Months	Postoperative Results, Time in Months	
			Dead	Living
50.....		1	..	95
51.....		1	8	..
53.....		1	6	..
45.....		4	18	..
42.....		1½	..	115
37.....		1	8	...
34.....		1½	59	...
32.....		2	8	...
35.....		1½	..	150
29.....		4	12	...
22.....		3	8	...
23.....		2	23	...
14.....		4	215*	...
12.....		3	42	...
8.....		3	58	...
2.....		4	108	...
Group B				
20.....		6	24	..
41.....		6	54	...
44.....		6	55	...
47.....		12	..	100
49.....		8	51	...
43.....		12	..	114
27.....		10	48	...
16.....		24	84	...
21.....		24	26	...
15.....		12	24	...
11.....		15	60	...
Group C				
33.....		36	13	...
28.....		30	..	184
4.....		60	5	...
3.....		48	66	...

\* Died of cancer of stomach.

TABLE 3.—*Postoperative Results in Cases in Class 3*

Case	Preoperative Time, Months	Postoperative Results, Time in Months	
		Dead	Living
38.....	60	36	..
36.....	12	6	..
31.....	156	36	..
25.....	4	30	..
17.....	36	6	..
9.....	42	60	..
6.....	24	22	..
1.....	12	2	..

patients died within five years after operation, six additional patients died following a recurrence from six to sixteen years after operation.

Of the remaining seven patients, six are alive and apparently free from recurrence seven years and ten months, eight years and ten months, fifteen years and six months, seventeen years and six months, twenty years and twenty years and six months, respectively, after operation. The seventh patient died of pneumonia at the age of 81, twelve years and six months after operation.

Although class 1 is composed of only fifteen cases, it offers sufficient data to demonstrate at least two points: (1) So-called five year cures represent a purely arbitrary standard which bears little relation to the ultimate results; (2) the postoperative prognosis of cancer of the breast is by no means as hopeless as has been suggested in some of the conclusions based on the analyses of known deaths following operations for cancer of the breast.

My records show that thirty-one cases belonged in class 2; i. e., the axillary glands were invaded at the time of operation, but there was no evidence of the involvement of any contiguous or distant organ or tissue. The results in this class present a sharp contrast to the results shown in class 1. Only ten (32 per cent) of the thirty-one patients survived the five year period. Three of the ten subsequently died of recurrent cancer. One patient died of cancer of the stomach seventeen years and eleven months after operation. Six patients (18 per cent) were still alive and apparently free from recurrences seven years and eleven months, nine years and seven months, twelve years and six months, eight years and six months, nine years and six months and fifteen years and four months, respectively, following operation.

When this series of cases was first reported, those in class 2 were subdivided into three groups: Group A was composed of cases clinically considered highly malignant, because within four months or less after discovery of the tumor more or less extensive axillary involvement was found at operation. The cases in group B were arbitrarily suspected of being less malignant than those in group A, because, although glandular metastases may actually have been present as early as four months after the discovery of the tumors, there was on the whole such an element of insidiousness about them that medical advice was not sought, and when the patients were seen from six months to two years after the tumors had been noted, the cases still definitely belonged in class 2. Group C was made up of cases that showed evidences of a low grade of malignancy. This classification was justified by the fact that from two and one-half to five years after the discovery of the tumors, they still belonged in class 2.

While the number of cases in these groups is not large enough to make the results more than suggestive, it is, nevertheless, interesting to

note that the average period from the time of the discovery of the tumor until death in group A, cases in which the patients died of cancer of the breast, was only twenty-eight months. In group B, cases clinically conceived to be of medium grade malignancy, the average duration of life from the time of the discovery of the tumor until death was sixty-one months. In group C, cases clinically conceived to be of low grade malignancy, the average duration of life from the time of the discovery of the tumor until death was seventy-nine months.

Case 14 deserves special mention because, although the patient died of cancer of the stomach seventeen years and eleven months after operation for cancer of the breast, the tumor of the stomach was apparently a typical primary cancer of the pylorus for which a palliative gastro-enterostomy was performed two years before death. At the time of the operation on the breast, this woman, aged 43, had an apparently rapidly growing, rapidly metastasizing tumor with extensive axillary involvement. I thought that the prognosis was especially bad. Thirteen months after operation, she gave birth to a child, which she nursed on the remaining breast. Eight and one-half years after operation an enormous swelling of the right arm developed; this persisted in spite of all attempts at treatment for about five years and then gradually subsided. When I next saw her, she was extremely emaciated as a result of a practically complete pyloric obstruction. Nevertheless, following a gastro-enterostomy, she improved and remained in fair health until shortly before her death.

One patient (case 28), the oldest survivor of the patients in the class 2 cases, in January 1934 was hale and hearty fifteen years and six months after operation. Her case was originally placed in group C, with a clinical estimate of low malignancy, because at the time of operation, two and one-half years after discovery of the tumor, it was found that the growth was still operable and that only a moderate axillary involvement was present.

In this series there were eight cases in class 3, namely, those with demonstrable involvement of organs other than the breast and the axillary glands. None of the patients survived the five year postoperative period, and all of them died of cancer. Although there are only eight cases in this group they indicate the extreme variability in the span of life of patients with this type of cancer.

In case 1, the patient died one year and two months following the discovery of the tumor. In case 31 the patient knew that she had cancer of the breast for thirteen years before she finally agreed to have an operation, and she lived for three years after operation. In case 9 the patient lived for eight years and six months; in case 38 the patient lived for eight years. In this class the average length of life after discovery of the tumor was sixty-eight months, which closely approxi-

mates the span of life in the cases in classes 1 and 2, in which the patient ultimately died of cancer (an average of sixty-two months).

### CONCLUSIONS

The prognosis in cancer of the breast is by no means hopeless. In favorable cases postoperative survival without demonstrable recurrence for over twenty years is by no means uncommon. While an arbitrary period, such as five years, may be useful for certain statistical purposes, nevertheless, in the cases of classes 1 and 2 in this series, among the patients who ultimately died of recurrence, twenty died within five years of operation and ten died five or more years after operation, the post-operative periods extending up to fifteen or sixteen years.

Notwithstanding the apparent cures in some cases, I have been forced to the conclusion that the ultimate prognosis in each case is, for the most part, determined by factors which in the present state of knowledge may be conceived of as the product of the degree of malignancy of the tumor and the resistance inherent in the patient. The woman who is fortunate enough to have a thorough operation performed for a slowly metastasizing tumor before glandular involvement has taken place stands an excellent chance of never having a recurrence or of living for many years without a demonstrable recurrence.

Surgery has little to offer the woman with a rapidly metastasizing tumor, because, even though she is operated on almost immediately after the tumor is discovered, she will probably die in a relatively short time. In the case of the slow-growing, less malignant tumor, even though operation is performed relatively late, the postoperative survival is liable to be prolonged in keeping with the course of the progress indicated previous to the operation.

Recognizing fully the desirability of developing laboratory methods for estimating the prognosis in cancer of the breast, I nevertheless wish to call attention again to the fact that in almost every case of cancer of the breast the surgeon has at his command readily available clinical methods by which he can estimate at least some of the factors regarding malignancy as shown by the behavior of the growth up to the time of operation. A study of the histories of the cases herein summarized and of other cases reported in the literature indicates that in the present state of knowledge the actual malignancy of a case can probably be most accurately judged by the careful observation of the extent of the growth and of the metastases at the time of operation and by the estimation of the rapidity of growth and the rate of the development of metastases in terms of the time which elapses between the discovery of the tumor and the operation.

## A BRONCHOBILIARY FISTULA

R. W. FRENCH, M.D.

FALL RIVER, MASS.

Accurate systems for recording data and follow-up clinics in many hospitals verify the excellent results of surgical intervention on the biliary tract.<sup>1</sup> A surgical accident with the results described here is rarely seen. The accompanying illustration indicates the injury which occurred to the common duct when the gallbladder was removed. The dotted lines show the gap between the stump of the common duct and the duodenum. The disturbance in the flow of bile resulted in cholangitis, a suppurating process in the subphrenic space and finally the formation of a fistulous tract between the bile ducts and the bronchial tree.

### REPORT OF A CASE

N. H., an English housewife, aged 31, thin and poorly nourished, was first admitted to the Truesdale Hospital on April 11, 1928. A year previously cholecystectomy was done at another hospital, and since that time the patient had suffered from general weakness and malaise and a biliary fistula. Three months prior to admission the fistula closed; the patient became jaundiced and suffered from intense itching. She began to lose weight.

Physical examination revealed a mass the size of a tennis ball in the right upper quadrant of the abdomen at the site of the previous operative scar.

Examination of the blood showed the hemoglobin content to be 75 per cent, the erythrocyte count 3,980 and the leukocyte count 10,600. The icterus index was 100.

Exploratory laparotomy disclosed extensive adhesions in the region of the gallbladder. A long search for the common duct proved fruitless, since through a surgical accident at the time of the cholecystectomy much of the common duct had been removed with the gallbladder. An unsuccessful attempt to reconstruct the common duct failed because only the distal part was found.

There was marked improvement in the patient's condition as bile drained freely through the sinus for several months. Four months later, however, with the cessation of drainage of the bile through the sinus, symptoms of itching and jaundice recurred. The patient was readmitted to the hospital. The sinus in the abdomen had closed. The icterus index was 50.

The patient was given calcium lactate and bile from pigs. The symptoms disappeared. The patient remained clinically well for eight months, with clear urine and bile in the stools.

A year later, in April 1929, she returned to the hospital. She had had three more attacks of jaundice accompanied by pain in the upper right quadrant of the abdomen, fever and chills. The icterus index was 60. A week later the patient was discharged improved. At this time her digestion and appetite were excellent, and bile had reappeared in the stools.

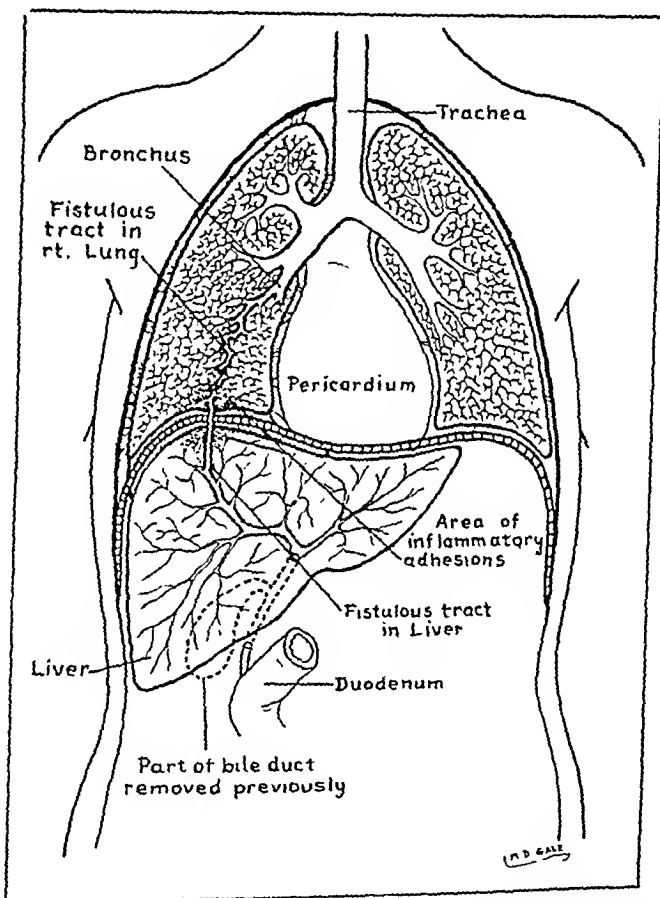
1. Whipple, A. O., in *Nelson Loose-Leaf Living Surgery*, New York, Thomas Nelson & Sons, 1928, vol. 5, p. 523.



In December 1929, eight months later, the patient was admitted for treatment of a severe dermatitis as a result of bile pigment. The hemoglobin content was 70 per cent, and the icterus index was 60, but the patient did not have any other symptoms of biliary obstruction.

Twenty months later, in September 1931, she returned complaining of a severe cough with copious expectoration of bile and excessive pain in the right costo-vertebral angle which radiated to the shoulder.

Roentgen examination at this time demonstrated a pleural effusion at the base of the right lung. Bile had entered the thorax as a result of a bronchobiliary fistula.



Drawing illustrating injury to the common duct when the gallbladder was removed. The dotted lines indicate the part of the bile tract removed three years previously when a cholecystectomy was performed.

It was decided to attempt to drain the bronchobiliary fistula by the abdominal route, as drainage of the liver below the diaphragm was thought to involve less risk of other complications. At operation the liver was markedly congested and purplish brown. No walled-off accumulation of bile below the diaphragm was found.

The patient's condition grew steadily worse, and she died on the third post-operative day.

Postmortem examination revealed that the lower lobe of the right lung was edematous and bile-stained. At the dome of the diaphragm on the right was a

fistulous tract through which a probe was passed to the lung and bronchus. At the dome of the right lobe of the liver was a degenerated area 1 cm. in diameter lying 6 cm. below the surface. This small space connected with a fistulous canal passing through the liver into the lung and communicating with the bronchus. The superior surface of the liver was irregular and adherent to the diaphragm. In the same region as the fistula but deeper within the liver substance were several areas of degeneration with soft centers and outside limits deeply yellow.

The gallbladder was absent. The duodenum was opened and the common duct traced upward. The duct was approximately 6 cm. in length and ended in a blind pocket. The hepatic duct was not found when the liver was sectioned, and the bile ducts were dissected downward to the hepatic duct. It was discovered that only 1 cm. of hepatic duct remained.

The pathologist's diagnosis was: absence of the hepatic duct and a portion of the common bile duct with right bronchobiliary fistula.

In March 1928, Morton and Phillips<sup>2</sup> published an extensive list of forty-nine cases of true bronchobiliary fistula in which bile ducts were prevented from emptying in their normal manner by an obstruction. To this series they added one case. In these fifty cases interference with the normal flow of bile was caused by obstructions such as gumma, cancer at the head of the pancreas, *Ascaris* worms or tuberculous processes in the lung and the liver. Three cases were the result of trauma. Stumpff's<sup>3</sup> patient was knocked down by a bicycle; in Graham's<sup>4</sup> case symptoms began after the patient had been kicked by a horse, and in Tyramen's<sup>5</sup> patient the fistula developed after shrapnel wounds and communicated with a ruptured bronchus through the torn edge of the diaphragm.

Since 1928, Seelig and Singer,<sup>6</sup> Meredith,<sup>7</sup> Loe,<sup>8</sup> Laird and Wilkerson,<sup>9</sup> Razemon<sup>10</sup> and Rácz<sup>11</sup> have each reported a case of bronchobiliary fistula. Loe's case was the result of trauma, the fistulous tract

2. Morton, J. J., and Phillips, E. W.: *Bronchobiliary Fistula: Review of Recorded Cases Other Than Those Due to Echinococcus and Amebic Ulcers*, Arch. Surg. **16**:697 (March) 1928.

3. Stumpff, quoted by Elliot, T. R., and Henry, H. G. M.: *Brit. M. J.* **1**:9, 1916.

4. Graham, J. E.: *Brit. M. J.* **1**:1397, 1897.

5. Tyramen, A.: *Arch. f. klin. Chir.* **89**:434, 1909.

6. Seelig, M. G., and Singer, J. J.: *Bronchobiliary Fistula*, Arch. Surg. **19**: 149 (July) 1929.

7. Meredith, E. W.: *Pennsylvania M. J.* **33**:389 (March) 1930.

8. Loe, A. O., and Loe, R. H.: *S. Clin. North America* **10**:1109 (Oct.) 1930.

9. Laird, W. R., and Wilkerson, W. V.: *Am. J. Surg.* **15**:317 (Feb.) 1932

10. Razemon, P.; Bizard, G., and Lambret, H.: *Echo méd. du nord* **36**:141 (March 19) 1932.

11. Rácz, B.: *Gyógyászat* **72**:621 (Oct. 8) 1932.

passing from the ruptured liver through the torn fibers of the diaphragm to the collapsed lung. Laird and Wilkerson and Razemon succeeded in outlining the fistulous tract by injecting iodized poppy-seed oil 40 per cent through the bronchoscope. In Razemon's case the diagnosis was arrived at solely through this means, since the patient presented few of the symptoms usually associated with bronchobiliary fistula. In Laird's case the oil demonstrated a hazy, irregular right diaphragm and a narrow shadow extending from the hilus into the obliterated right costophrenic angle. It was impossible to drain the common duct via the cystic duct because the latter had been completely obliterated through the formation of a subphrenic abscess.

A case which resembles the one reported here is that of Seelig and Singer. Their patient returned six months after a cholecystectomy with symptoms of general pruritus, diarrhea, nausea, prostration, jaundice and clay-colored stools. During the exploratory laparotomy the surgeon was unable to locate the common duct, and all of the landmarks were blotted out by dense adhesions. Between the stump of the common duct and the duodenum was a gap of 3.6 cm. A small catheter was fixed in the end of the common duct which led to the lumen of the duodenum. The patient was discharged three weeks after operation. She returned ten months later with a bronchobiliary fistula. A subphrenic abscess had perforated the diaphragm and established a fistula between the bronchus and the intrahepatic biliary capillaries. After spontaneous expulsion of bile and pus from the bronchi, the symptoms abated.

#### SUMMARY

Fifty-six cases of bronchobiliary fistula have been reviewed, in four of which the fistula was the result of trauma and in two, the sequel of a surgical accident. In the remainder of the cases the fistula occurred after obstruction of the biliary passages due to other causes.

The most common location of the fistula was through the dome of the diaphragm over the apex of the right lobe of the liver. Sometimes, however, collections of pus followed a more circuitous course in seeking an outlet.

Operative treatment afforded relief in the majority of cases if the operation was carried out in carefully planned stages. In a few cases the fistula healed spontaneously after the pus was evacuated from the bronchus and surrounding tissue.

Drainage of the fistula by the abdominal route involved less risk of further complications.

In two instances the injection of iodized poppy-seed oil into the fistulous tract was of valuable aid in diagnosis and in facilitating the problem of drainage.

# CHANGES OF THE BONES IN THE LEUKEMIAS

LLOYD F. CRAVER, M.D.

AND

MURRAY M. COPELAND, M.D.

NEW YORK

The literature is replete with instances of gross lesions of the bones associated with lymphoid and myeloid leukemia.<sup>1</sup> Many of the patients had unusual findings in the blood and an atypical histopathologic picture.

The following study presents the roentgenographic features of the changes of the bone which are associated with lymphoid and myeloid leukemia.

## LYMPHOID LEUKEMIA

Since 1917, eighty-six patients with lymphoid leukemia have been treated at the Memorial Hospital. Of this group, six patients (7 per cent) ultimately showed changes of the bones roentgenographically (table).

---

From the Memorial Hospital.

1. Craver, L. F., and Copeland, M. M.: *Arch. Surg.* **28**:809 (May) 1934. Eisenlohr, C.: *Virchows Arch. f. path. Anat.* **73**:56, 1878. Ellermann, V.: *Centralbl. f. allg. Path. u. path. Anat.* **34**:33, 1923. Emerson, C. P.: *Bull. Johns Hopkins Hosp.* **18**:71, 1907. Ewing, J.: *Neoplastic Diseases*, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 394. Feer, E.: *Jahrb. f. Kinderh.* **116**:155, 1927. Gliniski, L. K.: *Virchows Arch. f. path. Anat.* **171**:101, 1903. Gluzinsky, A., and Reichenstein, M.: *Wien. klin. Wchnschr.* **19**:336, 1906. Hauck, G.: *Virchows Arch. f. path. Anat.* **78**:475, 1879. Herbst, O.: *Monatschr. f. Kinderh.* **9**:447, 1910-1911. Hoffman, W. J., and Craver, L. F.: *J. A. M. A.* **97**:836 (Sept. 19) 1931. von Jaksch, R.: *Ztschr. f. Heilk.* **22**:259, 1901. Karshner, R. G.: *Am. J. Roentgenol.* **16**:405, 1926. Lehdorff, H., and Zak, E.: *Folia haemat.* **4**:636, 1907. Lundholm, L.: *Acta pædiat.* **9**:137, 1929. Melchior, E.: *Zentralbl. f. Chir.* **49**:1737, 1922. von Mullern, K., and Grossman, B.: *Beitr. z. path. Anat. u. z. allg. Path.* **52**:276, 1912. Nauwerck, C., and Moritz, P.: *Deutsches Arch. f. klin. Med.* **48**:558, 1905. Oesterlin, E.: *Virchows Arch. f. path. Anat.* **247**:589, 1923-1924. Paltauf, R.: *Wien. klin. Wchnschr.* **25**:46, 1912. Pförringer: *Fortschr. a. d. Geb. d. Röntgenstrahlen* **20**:405, 1913. Rolleston, H. D., and Frankau, C. H. S.: *Lancet* **1**:173, 1914. Runeberg, J. W.: *Deutsches Arch. f. klin. Med.* **33**:629, 1883. Schwarz, E.: *Ztschr. f. Heilk.* **22**:294, 1901. Sternberg, C.: *Myeloses*, in Henke, F., and Lubarsch, O.: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1926, vol. 1, p. 67. Taylor, H. K.: *Radiology* **6**:523, 1926. Trusen, M.: *Monatschr. f. Kinderh.* **50**:45, 1931. Versé: *Verhandl. d. deutsch. path. Gesellsch.* **14**:62, 1912. Waldstein: *Virchows Arch. f. path. Anat.* **91**:12, 1883. Wolf, C.: *Beitr. z. path. Anat. u. z. allg. Path.* **89**:151, 1932.

# Data on Seven Patients with Changes of the Bones Associated with Leukemia

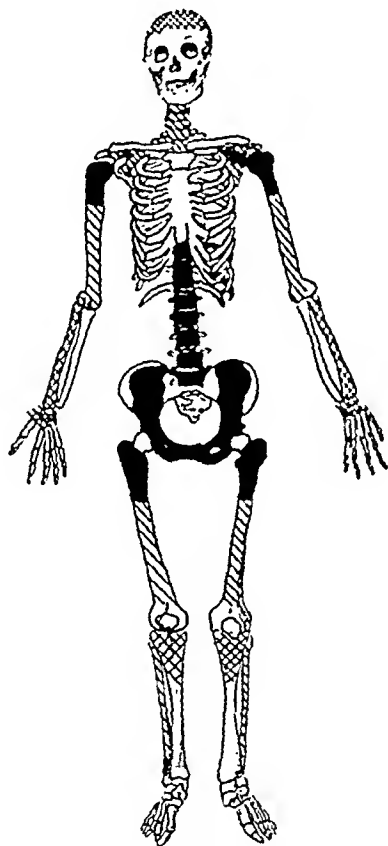
Case; Age, Years; Sex	Duration of Disease Prior to Changes of the Bones	Viscera and Nodes Demonstrably Involved	Bones Involved*	Treatment to Bones	Laboratory Findings †	Duration of Life Following Changes of the Bones
1. M. N. 3 F	2 months	Submaxillary, axillary and inguinal nodes; tonsils; liver; spleen	Left first metacarpal (C); left ulna (P and C)	8/12/26 to 8/27/26, high voltage roentgen therapy	7/26/26: Hgb., 20 per cent; R.B.C., 1,100,000; W.B.C., 8,050; P., 4; S.L., 94; My., 2..... Following transfusion and roentgen therapy 8/17/26: Hgb., 80 per cent; R.B.C., 4,200,000; W.B.C., 12,100; P., 47; S.L., 18; L.L., 29; My., 6	Dead after 2 months
2. C. C. 65 F	1 year, 3 months	Tonsils; spleen; cervical and bilateral axillary and inguinal nodes	Skull (P)(C)	2/7/30 to 5/14/31, high voltage roentgen therapy	6/ 7/29: Hgb., 20 per cent; R.B.C., 4,600,000; W.B.C., 10,300; P., 28; S.L., 59; L.L., 10; My., 3..... 1/12/31: Hgb., 75 per cent; R.B.C., 3,700,000; W.B.C., 6,900; P., 38; S.L., 55; L.L., 7 2/21/31: Hgb., 55 per cent; R.B.C., 2,900,000; W.B.C., 1,600; P., 57; S.L., 16; L.L., 16; Tr., 5; My., 6 Following transfusion 4/10/31: Hgb., 70 per cent; R.B.C., 3,300,000; W.B.C., 3,700; P., 47; S.L., 41; L.L., 9; Tr., 3 7/30/31: Hgb., 75 per cent; R.B.C., 3,700,000; W.B.C., 4,000; P., 53; S.L., 37; L.L., 34; Tr., 3; E., 3; Wassermann test, negative	Dead after 9 months, 2 weeks
3. P. H. 40 F	1 year, 3 months	Spleen; bilateral cervical infra-clavicular axillary and inguinal nodes	Pelvis (C); left femur (C)	Much radium and roentgen therapy	12/27/23: Hgb., 60 per cent; R.B.C., 3,200,000; W.B.C., 38,000; P., 45; S.L., 45; L.L., 7; My., 3..... 2/21/24: Hgb., 80 per cent; R.B.C., 4,200,000; W.B.C., 9,900; P., 72; S.L., 2; L.L., 26 4/10/24: Hgb., 70 per cent; R.B.C., 3,500,000; W.B.C., 4,600; P., 52; S.L., 48 9/25/24: Hgb., 55 per cent; R.B.C., 2,700,000; W.B.C., 17,200; P., 64; S.L., 14; L.L., 18 3/ 3/25: Hgb., 70 per cent; R.B.C., 4,800,000; W.B.C., 14,500; P., 59; S.L., 68; L.L., 2; My., 2 9/ 3/25: Hgb., 75 per cent; R.B.C., 4,800,000; W.B.C., 10,300; P., 53; S.L., 36; Tr., 4; My., 2 10/ 4/26: Hgb., 75 per cent; R.B.C., 3,600,000; W.B.C., 3,000; P., 63; S.L., 10; L.L., 9; Tr., 6; My., 4 11/ 4/26: Hgb., 60 per cent; R.B.C., 2,800,000; W.B.C., 2,400; P., 60; S.L., 24; L.L., 9; Tr., 7	Dead after 2 years 9 months
4. E. C. 32 F	1 year	Submaxillary and bilateral cervical, axillary and inguinal nodes; spleen and submental region	Left and right femur (P)	11/23/31, Heublein unit therapy, 15% E.D.; 6/9/32, Heublein unit therapy, 25% E.D.	5/1/31: Hgb., 80 per cent; R.B.C., 4,000,000; W.B.C., 12,100; P., 23; S.L., 71; L.L., 3; Tr., 3..... 5/21/31: Hgb., 60 per cent; R.B.C., 3,000,000; W.B.C., 5,400; P., 32; S.L., 53; L.L., 3; Tr., 11 12/ 2/31: Hgb., 80 per cent; R.B.C., 4,000,000; W.B.C., 4,700; P., 40; S.L., 49; L.L., 5; Tr., 4 6/ 9/32: Hgb., 80 per cent; R.B.C., 3,900,000; W.B.C., 3,000; P., 36; S.L., 43; L.L., 10; Tr., 3; E., 8; 9/28/32: W.B.C., 3,800; P., 47; S.L., 25; L.L., 4; Tr., 1; E., 2 Platelets, 292,000	Living after 2 years
5. R. H. 73 M	3 years, 8 months	Cervical and bilateral mediastinal, retroperitoneal, inguinal and femoral nodes; spleen	Right humerus (C)	11/13/31, Heublein unit therapy, 25% E.D.; 1/18/32, Heublein unit therapy, 27% E.D.	11/12/31: B.M.R., 69-80; Hgb., 75 per cent; R.B.C., 3,800,000; W.B.C., 6,000; P., 43; S.L., 22; L.L., 35 1/ 7/32: Hgb., 75 per cent; R.B.C., 3,800,000; W.B.C., 5,400; P., 53; S.L., 30; L.L., 12 6/ 9/32: Hgb., 65 per cent; R.B.C., 3,400,000; W.B.C., 8,300; P., 55; S.L., 5; L.L., 4; Tr., 3; My., 3 8/18/32: W.B.C., 5,600; P., 53; S.L., 33; L.L., 5; Tr., 3; My., 2 9/18/32: B.-J.B. none	Died at 4 months (autopsy: pseudo-leukemia)
6. A. G. 73 M	2 years, 4 months	Spleen; cervical and bilateral axillary and inguinal nodes; tonsils	Eleventh thoracic vertebra (C)	2/20/33, high voltage roentgen therapy	2/ 2/30: Hgb., 85 per cent; R.B.C., 4,500,000; W.B.C., 43,200; P., 17; S.L., 72; L.L., 15; Tr., 1..... 12/ 3/31: Hgb., 80 per cent; R.B.C., 4,100,000; W.B.C., 11,700; P., 49; S.L., 44; L.L., 9; Tr., 2 2/10/31: Hgb., 80 per cent; R.B.C., 3,900,000; W.B.C., 7,400; P., 40; S.L., 44; L.L., 7; Tr., 3; E., 2 2/17/33: Hgb., 75 per cent; R.B.C., 3,600,000; W.B.C., 11,900; P., 39; S.L., 48; L.L., 7; Tr., 2; E., 4	Living after 3 months
7. H. M. 59 F	8 months	Cervical and bilateral inguinal nodes; liver	Right humerus (C); right femur (C); left femur (C)	No treatment to bones	5/19/32: Hgb., 100 per cent (Dare); R.B.C., 6,000,000; W.B.C., 5,500; P., 54; S.L., 3.5; B., 3.5; My., 23; Mybl., 11.5; E.M.V., 3 5/26/32: W.B.C., 34,000; P., 64; S.L., 14; My., 16.5; E.M.V., 3.5; B.M.V., 4.5 5/31/32: W.B.C., 20,500; P., 75.5; S.L., 5; E.M.V., 1; B., 1.5; My., 17	Living after 9 months

\* Osteoplastia is indicated by C and osteoplastic by P. R.B.C.: white blood cells, by W.B.C.; polymorphonuclears, by P.; small lymphocytes, by S.L.; large lymphocytes, by L.L.; monocytes, by M.; transitional, by Tr.; basal metaphase rate, by B.M.R.; radiophosphorus, by R.P.; myeloblasts, by Mybl.; eosinophils, by E.; erythroid doses, by E.D.; bone marrow, by B.-J.B.

Four of the patients were over 40 years of age.

There were four female and two male patients.

The duration of the disease prior to demonstrable changes of the bones varied from two months to three years and eight months. Following osseous involvement, one patient (case 4) is living after two years, and three died within one year. Apparently there is no correlation



The black areas represent the most frequent sites of changes in the bones; the checkered areas, the next most common sites; the diagonal lines, the sites occasionally involved, and the white areas, the sites rarely affected.

between the early development of changes of the bones and the duration of life following them.

The symptoms were pain and, not infrequently, swelling over the affected bones, associated with other features of the disease. In some instances, no symptoms were noted in the affected bones. The pain was usually localized and was either severe or dull. Tenderness on pressure over the diseased bones was also a feature.

The clinical course, except as noted later, was generally characteristic of the disease and showed moderate enlargement of the spleen, involvement of the lymph nodes, fatigue, cachexia, anemia and increase in the lymphocytes of the blood, with early cell forms.

In a previous communication on changes of the bones seen in lymphosarcoma, it was pointed out that definite lymphoid leukemic changes in the blood occasionally supervene as a terminal phase of the disease. This might be termed leukosarcomatosis.<sup>2</sup>

In a number of cases observed at the Memorial Hospital in which the blood showed a relative increase in lymphocytes without early forms there was a clinical picture of lymphosarcoma. Only as a terminal feature of the disease were definite leukemic changes in the blood noted in some of the cases. The lymph nodes frequently showed a microscopic picture typical of lymphosarcoma.

All of the patients with changes of the bones showed a variation in the blood picture from that seen in typical lymphatic leukemia. The hemoglobin varied from 20 to 90 per cent. It usually improved with the proper control of the disease by irradiation. The red cell count varied between 1,000,000 and 4,500,000. The white cell count ranged from leukopenia to marked leukocytosis (table). Depending largely on the time of roentgen therapy, the differential count showed a return to a normal ratio or a continued increase in lymphocytic forms.

In case 5, in which autopsy revealed pseudoleukemia, repeated tests of the urine for Bence-Jones bodies gave negative results.

*Roentgenographic Study.*—A review of the literature showed that the incidence of involvement was greater in the bones normally containing red marrow, such as the ribs, spine and skull.

In this group of cases, the principal bones involved, in the order of frequency, were the femur, the humerus, pelvis, skull, metacarpals, ulna and vertebrae (illustration and table).

The roentgenograms showed both osteoclastic and osteosclerotic changes. A periosteal reaction was present in two cases.

The skull in case 2 showed a periosteal elevation, which could be felt on palpation in the frontal and parietal regions. Possible slight osteoporotic changes were also noted in the skull. No instance of involvement of the ribs was present in this group of cases.

The left ulna in case 1 presented definite periosteal lifting. The first metacarpal of the left hand showed expansion with marked osteoporosis.

---

2. Craver, L. F., and Copeland, M. M.: Lymphosarcoma in Bone, Arch. Surg. 28:809 (May) 1934.

The pelvis in case 3 was mottled with areas of decreased density.

The left femur in case 3 showed localized rarefaction in the lower diaphyseal region.

In general, osteoporosis predominated in all of the bones showing changes roentgenographically.

In reviewing this group of cases of lymphatic leukemia with gross changes of the bones it seems worthy of note that all were somewhat atypical in respect to the blood count. The patient in case 5 never showed a leukemic blood count, although the clinical picture otherwise was that of chronic lymphatic leukemia. Two lymph nodes from this patient showed a structure indistinguishable from that of a leukemic node, and at autopsy the observations, in view of the clinical course, were considered indicative of lymphatic pseudoleukemia. The condition in cases 2 and 4 may be termed low grade lymphatic leukemia. Case 1 was that of a child, aged 3 years, whose white cell counts were only 8,000 and 12,000. Cases 3 and 6 were the only ones in which there was marked leukocytosis, and in these cases the highest white cell count was only 38,600 and 43,200, respectively.

It may be, therefore, that gross involvement of the bones is of more frequent occurrence in low grade lymphatic leukemia than in cases with high white cell counts.

#### MYELOID LEUKEMIA

Of eighty-two patients with the myeloid type of leukemia, only one had associated changes of the bones.<sup>3</sup> The age of this patient, a woman, was 59 years (table).

The duration of the disease prior to the appearance of the changes of the bones was eight months. This patient is living nine months after the development of definite skeletal changes.

The symptoms associated with the changes of the bones in the cases of myeloid leukemia were similar to those recorded for lymphatic leukemia.

The clinical course was similar to that seen in the general group of cases of myeloid leukemia. The blood picture (table) showed a hemoglobin content of from 75 to 109 per cent. The white cell count varied from 5,000 to 34,000. Myelocytes were a constant feature.

*Roentgenographic Study.*—The changes of the bones in myeloid leukemia are usually those of osteoporosis or osteosclerosis with diffuse

3. Ewing, J.: *Neoplastic Diseases*, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 394.



or localized areas of rarefaction. Cases with periostitis have been reported.<sup>4</sup>

The femurs in case 7 showed mottling in the upper thirds. Central punched-out lesions were observed in the femurs.

Early lesions are difficult to evaluate, and many are not demonstrable in the roentgen films. Variations in roentgenographic technic should be carefully discounted in giving an opinion.

#### PATHOLOGY

In studies of the bones of the patients with lymphoid and myeloid leukemia, the bone marrow usually showed the process beginning as hyperplastic foci which enlarged and coalesced, eventually extending throughout the marrow-containing portion of the bone. The spongy trabeculae were then attacked and found to be in various stages of absorption. The shafts seemed to be thinned, and in places a distinctly aggressive destruction of the bone was seen.

Microscopic studies of the osseous erosions showed resorption of bone with plugging of the haversian canals by the leukemic process. The erosion seemed to be due to the leukemic process per se rather than to the loss of blood supply caused by the occlusion of the haversian canals.

It is important to emphasize the large numbers of erosions of the medullary bone which were found at autopsy but which could not be demonstrated in roentgen films. This compels one to conclude that changes seen roentgenographically represent relatively late changes in the bony structure. On the other hand, it is our opinion that changes might be demonstrated roentgenographically in a higher percentage of cases of leukemia than our figures indicate. Roentgen studies of the skeleton have not hitherto been made as a routine in cases of leukemia.

*Differential Diagnosis.*—The changes of the bones in the leukemias are to be differentiated from carcinoma, multiple myeloma, Hodgkin's granuloma, lymphosarcoma and osteomyelitis.

Metastatic lesions of the bone are usually medullary and most frequently appear at the sites where the vessels enter or emerge from the bone. Carcinoma of the prostate and of the breast may give rise to metastases which stimulate an osteoplastic reaction. Rarely does one see the diffuse osteoporosis found in leukemia associated with metastatic lesions.

Multiple myeloma may readily be confused with the osseous changes in leukemia. The blood count and the involvement of the spleen and lymph nodes are valuable findings in differentiating the two diseases.

---

4. von Jaksch, R.: Multiple Periostitis and Blood Findings Suggesting Myeloid Leukemia, *Ztschr. f. Heilk.* 22:259, 1901.

Bence-Jones bodies are found in 65 per cent of cases of multiple myeloma although they are rare in cases of leukemia.

In Hodgkin's granuloma and lymphosarcoma involving bone, a blood count and biopsy of a lymph node are important in making the diagnosis. In certain cases of lymphosarcoma, a terminal leukemic blood picture may supervene.<sup>2</sup>

In osteomyelitis, periostitis is a common finding, but the reaction is much more extensive, and the periosteal changes give a shaggy appearance to the lesion. Leukocytosis is usually found in osteomyelitis, but atypical blood forms are rare. The involvement of the spleen and lymph nodes found in the leukemias is important in differentiating the two diseases.

#### TREATMENT

High voltage roentgen therapy in suberythema doses applied to the diseased bone is efficacious in relieving pain and often permits complete repair of the bone. External radium therapy has also been used with good results.

In treating large numbers of patients in clinics such as that of the Memorial Hospital, it has been found economically desirable to treat the majority of patients with leukemia by roentgen therapy, and in so doing it has been shown that roentgen therapy offers as much in the way of palliation as does radium therapy.

More recently, irradiation by high voltage roentgen rays at longer distances has proved beneficial in the treatment of the leukemias, especially lymphoid leukemia. This therapy is administered to the entire body or to certain portions of the body selected for treatment. The dosage to the entire body should rarely exceed 120 roentgen (r) units in one course of treatment.

Supportive therapy, such as a diet rich in iron, liver or liver extract and, in selected cases, small transfusions, may be a distinct contribution in the care of the patient.

#### SUMMARY

Eighty-six cases of lymphoid leukemia were analyzed, and six patients (7 per cent) were found to have associated gross changes of the bones which were demonstrable by roentgen examination.

Eighty-three cases of myeloid leukemia were analyzed, and one patient was found to have gross changes of the bones.

The changes of the bones in general were found to be either osteoporotic or osteosclerotic, with or without periostitis.

The general course of the disease is no different from that usually seen in cases of lymphoid and myeloid leukemia.

The urine of one patient was studied for Bence-Jones bodies, with negative results.

The patients with lymphoid leukemia were often of the aleukemic type, while the patients with myeloid leukemia had definitely increased leukocyte counts.

The treatment is discussed.

# MEDIAN CLEFT OF LOWER LIP AND MANDIBLE, CLEFT STERNUM AND ABSENCE OF BASHIYOID

## REPORT OF A CASE

CHARLES BRUCE MORTON, M.D.  
Assistant Professor of Surgery and Gynecology

AND

HARVEY ERNEST JORDAN, Ph.D.  
Professor of Histology and Embryology  
UNIVERSITY, VA.

Inferior gnathoschisis is an extremely rare anomaly. Search of the literature has revealed only three instances of this defect in man. Keith<sup>1</sup> recorded a case in a full term infant (MacCornick's specimen in the museum at St. George's Hospital). Dupuytren<sup>2</sup> mentioned a case of "median fissure of the lower lip and lower jaw." Wölfler<sup>3</sup> described a similar case in which there was, in addition, a cleft tongue. Hamilton<sup>4</sup> and Bland-Sutton<sup>2</sup> each reported a case of partially cleft lower lip.

The defect is apparently equally rare in the lower animals. Walker<sup>2</sup> reported a median cleft of the lower lip, the lower jaw and the tongue in a calf. According to Keith the collection of examples of facial malformation in the museum of St. George's College includes only three specimens of median cleft of the lower lip and jaw; one from an ass, another from a cockatoo and a third from a sparrow.

In Wölfler's case of an infant of 23 days, the defect was corrected by operation, which added interest. McCurdy<sup>4</sup> gave a brief description of the malformation in this case and of the operative procedure:

The lower lip was split in the median line into two halves, which were again connected by cicatricial bridge in the lip proper. The latter, more strongly developed in its upper part and drawn toward the oral cavity, extended into the median line of the chin and into the neck down to the suprasternal fossa, becoming narrow and flatter as it descended. The cicatricial fissure in the lip corresponded to a defect in the lower jaw itself. This consisted of two halves, which were united by loose connective tissue and ran downward toward the median line.

---

From the University of Virginia.

1. Keith, Arthur, quoted by Brophy, T. W.: *Oral Surgery*, Philadelphia, P. Blakiston's Son & Co., 1915, p. 559.

2. Quoted by Paget, S.: *Malformations of the Lower Lip*, *Lancet* 2:476, 1892.

3. Wölfler, Anton, quoted by McCurdy.<sup>4</sup>

4. McCurdy, S.: *Oral Surgery*, Pittsburgh, Calumet Publishing Company, 1901, p. 170.

The movable median ends of the two halves of the lower jaw were decidedly thinned, narrowed and terminated in a rounded and flat extremity. More interesting yet was the condition of the tongue; the anterior portion was divided longitudinally in two halves, like the leaves of an open book. The mobility of these two halves was much interfered with by the adhesion of a median cicatrix, at the bottom of the fissure, to the floor of the mouth. The base of the tongue was not split. It was, therefore, a median cleft of the lower lip, involving the lower jaw and tongue, the lateral halves being held together at a distance by a cicatrix formation.

After a period of six months, operative treatment was determined upon. After splitting the cicatricial bridge, connecting the two halves of the lower lip and lower jaw, the cicatrix of the tongue running into the median line was first dissected from the floor of the mouth. The tongue was thus divided into two longitudinal halves, which, after removal of the cicatricial edges, were sutured, whereby the normal form of the tongue was restored. Then two pieces, each one centimeter wide, were removed from the ends of the jaw in order to obtain fresh bone surfaces, and united by means of silver wire. Finally the edges of the soft parts of the lower lip were freshened and sutured à la Mirault-Langenbeck. The healing of the wound progressed uninterruptedly. A small and final operation was required and performed for the correction of the cicatrix of the chin drawn into the groove at the lower end of the united lower maxillary.

The rareness of inferior gnathoschisis makes desirable the detailed description of additional cases. The malformation in our patient at the University of Virginia Hospital was extreme and was similar to that of Wölfler.<sup>3</sup>

#### REPORT OF CASE

*History.*—R. N. M., a white girl aged 13 days, was admitted to the University of Virginia Hospital on June 2, 1932. Her parents brought her for treatment of a congenitally cleft lower lip and jaw.

The child's family history was entirely unimportant. She was the tenth child born to her mother by the same father. All the previous children were said to be healthy and normal in every respect. Her parents were healthy, well nourished and apparently normal both physically and mentally. No congenital deformities were known to have occurred in any preceding generations or in any collateral relatives. The mother was delivered of the child uneventfully at full term by a midwife.

*Examination.*—The child was well nourished and seemed to be healthy and normal in every respect except for an apparently imperforate hymen and a congenital cleft commencing with the lower lip and extending to a point midway down the sternum.

The character of the deformity may be seen in figure 1. The nose, the upper lip, the upper alveolus, the hard palate, the soft palate and the uvula were entirely normal. The lower lip, the chin, the mandible and the floor of the mouth were cleft. The tongue was interposed between the two sides of the divided structures, and the end was attached by tough, dense fibrous tissue to the thin, delicate tissue of the neck. The entire undersurface of the tongue was attached to the divided floor of the mouth. The tip of the tongue was adherent so far down on the neck

that it accentuated and depressed the median raphe of the tongue in such a way that the tongue itself appeared to be cleft. When the edges of the actual cleft were separated, however, it became evident that the tongue was intact, though its end was spread out along the margins of the cleft in the chin and upper part of the neck and hence seemed unusually wide.

Under the chin was a peculiar pink, triangular area which did not seem to be entirely epitheliated. The base of the triangle extended along the lower border of the chin, and its apex was situated at the junction of the middle and lower third of the sternum. Part of the area was covered by a filmy, delicate epithelium, but other parts seemed to be unepitheliated. The corium was obviously lacking over the entire triangle. Cordlike prominences were evident just beneath the surface; presumably they represented the anterior muscles of the neck. The hyoid bone and the thyroid gland were not palpable. The larynx could be felt



Fig. 1.—*A*, photograph showing the child with gnathoschisis, in repose. *B*, the nose, upper lip, upper alveolus and palate were normal, and the lower lip, mandible and sternum were cleft. Note the deformity of the tongue, simulating a cleft.

by deep palpation, and phonation was normal. The entire manubrium and upper half of the sternum were apparently lacking. The sternal ends of the clavicles and ribs were consequently widely separated and movable. The sternocleidomastoid muscles were attached to the ends of the clavicles, and the movements of the head seemed to be normal. In repose the triangular area was depressed except for the cordlike muscles, which stood out more prominently. At each inspiration the depression was accentuated, while at each expiration the depression was slightly decreased. When the child cried or otherwise forcibly increased the intrathoracic pressure the triangular area bulged greatly. There was tympany, which suggested that the bulge was due to underlying lung tissue. The thymus was not identified. Roentgenograms of the entire body were made, but no deformities other than those described were found in the bones.

The child was able to nurse either from the breast or from a bottle fairly satisfactorily, though there was marked drooling at all times. This kept the entire area constantly moist and somewhat macerated. The child's general condition was so good that operation seemed desirable without delay.

*Operative Treatment.*—On June 7, 1932, with the child under ether anesthesia, the first operation was performed. The tongue was freed from its attachment to the neck and the margins of the cleft by sharp dissection. By excising a wedge of tissue with its base at the tip of the tongue and its apex posteriorly and another wedge with its base on the undersurface of the tongue and its apex superiorly, it was possible to reconstruct and epitheliate by suture a nearly normal-looking tongue. The tissue of the floor of the mouth under the tongue was approximated and epitheliated by suture. The ununited ends of the mandible

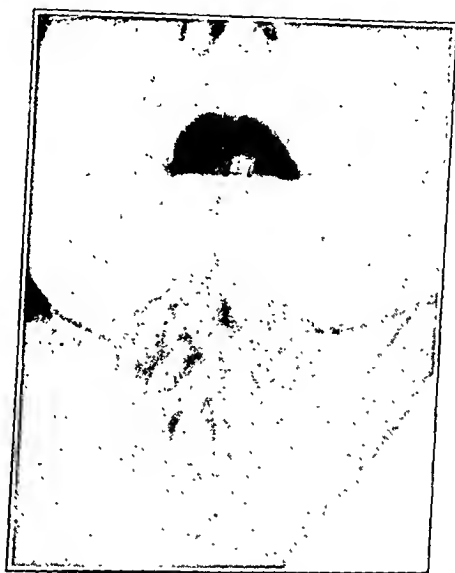


Fig. 2.—A photograph showing the immediate postoperative result (ten days). Note the normally mobile tongue, the scar of approximation of the two halves of the chin and the marked bulging in the region of the sternal defect due to increased intrathoracic pressure when crying.

were approximated by sutures placed in the soft tissues only. The child stood the operative procedure well, but it seemed safer to complete the repair at a later date.

The postoperative convalescence was uneventful, and the child continued to thrive. In a few days the tongue appeared to be almost normal and functioned normally.

The second operation was performed on June 25, 1932. With the patient under ether anesthesia, the edges of the cleft in the lower lip and chin were excised, and the contour of the lip and chin were restored to relatively normal appearance by suture (fig. 2).

The child's convalescence from this operation was uneventful. The structures healed by primary union, and both anatomically and esthetically the result was satisfactory. Several days later the child was taken home. The parents were directed to keep closely in touch with us, and plans were made to complete the plastic work at a later time by a whole thickness skin graft and subsequent bone graft at the site of the sternal defect.

*Result.*—The child was brought in for examination in January 1933, approximately six months after the operation. At that time directions were given the parents regarding improvement of the child's diet. A photograph taken at that time shows the relatively normal appearance of the face (fig. 3).

A letter, dated March 27, 1934, from the child's parents, stated that she died on Jan. 30, 1934, of pneumonia which followed measles. Prior to this acute illness the child seemed to be perfectly well and thrived normally. Postmortem examination unfortunately could not be made.



Fig. 3.—A photograph of the remote postoperative result (six months). Note the relatively normal-looking lower lip and chin. The shadow in the depression is at the site of the sternal defect.

#### COMMENT

The etiology of the condition involves three interesting questions: the embryologic interpretation in terms of primordia of the primitive pharynx; the nature of the factor underlying the developmental arrest, and the explanation of the relative infrequency of cleft of the inferior maxilla as compared with that of the superior maxilla. Obviously the primary defect concerns the mandible; defects in the tongue, the lip, the chin, the submental area of the skin, the body of the hyoid and the anterior half of the sternum are secondary. In our case the inhibitory factor prevented the normal medial union of the bilateral pair of mandibular primordia, the mandibular processes of the first pair of branchial arches; the resulting anomalous cleft in the primitive mandible disturbed





Under these conditions a bifid tongue was to be expected. The fact that the tongue was approximately normal except for its firm attachment medially to the floor of the mandibular cleft is puzzling. However, the tongue as bound down to the floor of the cleft appeared to be double anteriorly and was deeply creased in the midline. This bilaterally paired condition indicates the original pair of anterior tongue primordia. These primordia constitute the superficial oral portions of the mandibular processes. Since these processes failed to unite, the tongue primordia would also be expected to remain unfused and consequently to produce a split tongue. One can only conclude that the anterior tongue primordia were sufficiently closely approximated medially to permit of at least such a degree of fusion as could subsequently be improved by regulatory processes and result in a fairly normal uncleft tongue.

The midventral fusion of the branchial arches proceeds in a cephalocaudal direction. The nonfusion of the dominating mandibular processes of the first pair of arches may be assumed to have held apart the ventral ends of the succeeding arches. The restraint on the second and succeeding arches may be interpreted as the mechanical effect of the spread of the mandibular processes. The photograph of the postoperative result shows an approximately normal width of the lower jaw and chin. The mandibular cleft was apparently not the result of any lack of tissue but of the operation of some factor preventing contact of the opposed ends of the mandibular processes. In view of this, an alternative explanation of the submental cleft and the absence of the basihyoid may be given in similar terms. The same factor which hindered the approximation and union of the mandibular processes may have held apart also the opposed ends of the lower branchial arches. Since the body of the hyoid develops from the ventral area of fusion between the ends of the second and third pairs of branchial arches, the absence of a basihyoid is explainable also on the basis of a failure on the part of these two pairs of arches to become approximated in the midline. The same interpretation of mechanical resistance to median apposition of arch primordia may explain the defective integument and musculature over the anterior surface of the neck. The thin median area represents the original ventral pharyngeal region which remained uninvaded by branchial arch mesenchyme.

The anterior portion of the sternum was cleft, and the manubrium appeared to be entirely lacking. The bifid portion of the sternum corresponded in extent approximately to the defective area of the neck and adjacent portion of the chest. The body of the sternum arises from a bilateral pair of cartilaginous sternal bars, which fuse medially during the ninth week. The manubrium arises from a pair of presternal cartilages opposite the ventral ends of the clavicles. The bifid condition of the upper end of the sternum in this case was obviously the result

of a failure of cephalomedial fusion between the pair of sternal bars and between the adjacent manubrial cartilages. The episternal (manubrial) cartilages have presumably become attached either to the adjacent ends of the clavicles or to the cephalic ends of the bifid sternum. At the ninth week, when the paired primordia of the sternum normally fuse, the lower jaw is already relatively well developed. The median separation in the lower jaw in our patient may be assumed to have prevented the normal approximation of subjacent bilateral paired primordia and thus to have inhibited the normal development of the anterior half of the sternum.

This interpretation, then, that this group of medial clefts in structures which require for normal development orderly medial fusion of the respective mesenchymal primordia was the product of some factor inhibitory to the normal medial approximation of the ventral ends of the primordia calls for an identification of the nature of the repressive influence. The view that these defects are not the result of the lack of actual primordial tissue or even of deficient ventromedial elongation of the paired primordia, the embryonic branchial arches, may explain also the absence of a terminal cleft in the tongue. The anterior tongue primordia in our case were presumably of normal extent, and since the primordia are located on the oral surface of the mandibular processes and the wide portion of the mandibular cleft is in the region of the chin, they were not sufficiently widely separated to prevent a nearly normal degree of medial fusion.

In our search for the factor which prevented the approximation and fusion of the ventromedial ends of the mandibular processes, resulting in the wide cleft of the lower jaw, we were logically led to a stage just preceding the time of fusion of the mandibular processes, namely, to a point in time at the beginning of the fifth week. This stage of development is represented by an embryo approximately 5 mm. in length (fig. 5). At this stage the head end of the embryo is sharply flexed in the cervical region; the ventral surface of the pharynx is pressed down on the cephalic surface of the heart. Corresponding with the relatively thin midventral region of the pharynx, the area of approximating but unfused ventral ends of the mesenchymal branchial arches, is the aortic bulb (anteriorly) and the continuous truncus arteriosus. One needs only to postulate some factor of pressure producing a closer approximation than normal between the thin midventral surface of the pharynx and the subjacent anterior cardiac region to explain the lack of ventral fusion between the ends of the paired mandibular processes. Such approximation under pressure between the pharynx and the subjacent supracardiac wall of the body would produce a certain degree of more or less transient adhesion between the apposed structures. Adhesion could possibly be the primary factor rather than a secondary effect of

compression. The factor of adhesion, whether of secondary or of primary significance, helps further to explain the binding down of the chin to the subjacent region of the neck (which was conspicuous in the side view of our patient) and possibly in part explains the integumentary and muscular maldevelopment in the region of the anterior portion of the neck and upper part of the breast.

An analysis of the essential data, then, leads to the conclusion that the primary factor in this case was mechanical. The compression of the ventral pharyngeal region onto the anterior cardiac region at the 5 mm. stage (from 30 to 35 days) and/or adhesion between these two apposed surfaces along the midarea prevented fusion of the ventro-

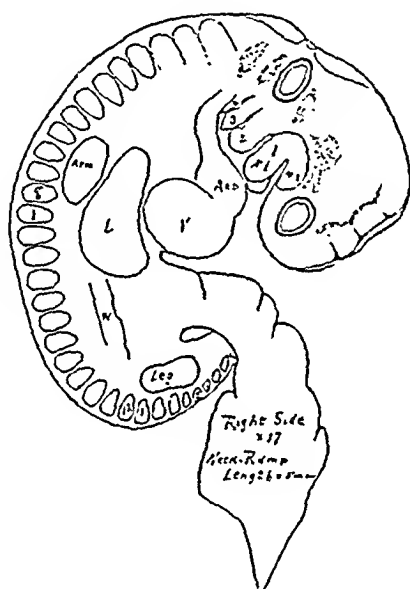


Fig. 5.—A drawing of the right side of Watts' embryo, at approximately the 35 day stage (from Jordan and Kindred: *A Textbook of Embryology*, New York, D. Appleton & Company, 1930).

medial ends of the paired mandibular processes and of the succeeding pairs of branchial arches, producing in consequence primarily a medial mandibular cleft and secondarily an anteriorly cleft sternum and a medial cervical area of defective skin and musculature.

This explanation of the anomaly, however, it must be admitted, only deepens the mystery of the rarity of the occurrence of clefts in the inferior maxilla. If this simple mechanical explanation sufficed, the anomaly should be expected to occur much more frequently. Assuming that the explanation is correct, as the anatomic and embryologic evidence outlined seems to indicate, then the extreme rarity of the defect may have its explanation in the fact that fusion between the midventral

pharyngeal region and the subjacent cardiac region, other than that of very slight degree, would almost certainly result in such serious interference with the normal cardiac function as to produce death and abortion before the beginning of the third month. An examination of aborted embryos of this period might reveal previously unrecognized instances of potential inferior gnathoschisis. Under this interpretation the cases of simple median cleft of the lower lip would represent conditions of the least degree of transient compression and fusion between the pharyngeal wall and the supracardiac integument.

#### SUMMARY

A review of the literature revealed that inferior gnathoschisis is an extremely rare anomaly. Only three instances of complete gnathoschisis in man, two instances of partially cleft lower lip in man and three instances of gnathoschisis in animals were found.

The case of a child with a median cleft of the lower lip and mandible, associated with a cleft sternum and absence of the basihyoid has been described in detail, together with the operative procedure employed to correct the deformity. The embryologic factors involved have been discussed.

# CONGENITAL ABSENCE OF THE SACRUM

W. R. HAMSA, M.D.

IOWA CITY

Defects of the caudal end of the vertebral spine are not so uncommon as one would imagine if judging from the literature. This deformity has been considered and reported more frequently in recent years, but it has had scanty mention when compared with the frequent reports of deformities in other parts of the spine, for instance, the Klippel-Feil syndrome. A plausible explanation is that deformities of the caudal portion of the vertebral spine are usually combined with extensive involvement of the viscera and the lower extremities and are not compatible with life and that hence they are of more theoretical anatomic interest. Many of the peculiar sirenes belong to this group. As a rule, these conditions show, in addition to the malformation of the lower extremities, considerable numerical reduction of vertebral segments, either complete, involving vertebral bodies and arches, or incomplete, with partial development of some of the segments. However, there are cases in which the degree of deformity of the caudal portion of the vertebral spine is compatible with life, and it is with these that the following pages are concerned.

A search of the literature revealed reports of only eighteen cases, and so the presentation of two others seems justified. Dr. Steindler permitted me to report these two cases.

Because of the few reports in the literature, a brief presentation in their chronological order is of interest.

Wertheim<sup>1</sup> reported the case of a girl, aged 8 days, who died of severe loss of weight; the spine ended at the fifth lumbar vertebra, and the sacrum and coccyx were missing.

Albrecht's<sup>2</sup> specimen showed a normal first sacral and a hypoplastic second sacral vertebra; the rest of the sacrum and coccyx were absent.

Litzmann<sup>3</sup> reported the case of a woman, aged 36, who had had deformity and weakness of the feet from birth. The feet were in the calcaneous position. The patient was incontinent. She had had two previous pregnancies; both of the infants were stillborn. The patient

---

From the Department of Orthopedic Surgery, University of Iowa, service of Dr. Arthur Steindler.

1. Wertheim, C. C.: Complete Absence of Sacrum and Coccyx in New-Born, *Monatschr. f. Geburtsh. u. Frauenkr.* 9:127, 1857.

2. Albrecht: Ueber congenitalen Defekt der drei letzten Sacral- und sammtlicher Steisswirbel, *Deutsche med. Wchnschr.* 11:413, 1885.

3. Litzmann: Ein durch mangelhafte Entwicklung des Kreuzbeines verengtes Becken, *Arch. f. Gynäk.* 25:31, 1884.

died during the third labor; the first two sacral segments alone were present and formed a semicircle which permitted bony union of the lumbar spine to the iliac wings; there were a sacralized third lumbar vertebra and malformed third and fourth lumbar vertebrae; the pelvis had a small transverse diameter.

Mally<sup>4</sup> reported the case of a child, aged 9 years, who had Little's syndrome, club feet, dislocation of the hip and absence of the sacrum and coccyx.

Friedel<sup>5</sup> reported the case of a full term child of undetermined sex who died following trauma occurring at birth. Rupture of the skin of the popliteal fossa with infection and erosion of the popliteal vein had occurred; the vagina was rudimentary; the right foot was in the calcaneus, and the left in the equinus position. The spine ended at the tenth dorsal segment. The ischial spines were fused.

Fitch's<sup>6</sup> case was that of a boy, aged 6 years, who stumbled easily and who was incontinent; there were anomalies of the lower cervical and the upper dorsal portion of the spine. The lower four sacral segments and the coccyx were absent.

White's<sup>7</sup> patient was a full term, stillborn boy with atresia of the rectum and anus; both feet were in the equinovarus position, and there were severe abdominal malformations. The two lumbar vertebrae were rudimentary. The rest of the spine caudally was absent.

Charlier and Sauty<sup>8</sup> reported the case of a 4 month old boy with a large spina bifida manifesta. He was incontinent. The right foot was in the equinovarus, and the left in the calcaneovalgus position. Death followed the removal of a meningocele. There were right dorsolumbar scoliosis and extensive spina bifida caudally from the tenth dorsal vertebra. The sacrum and coccyx were absent.

Rendu and Verrier's<sup>9</sup> patient was a child, aged 1½ years, who was incontinent and who had partial paralysis of the lower extremities. The right foot was in the equinovarus, and the left in the calcaneovalgus position. There was dislocation of the hips; the fifth lumbar vertebra was substituted for the first sacral vertebra, and the sacrum was represented by a small bony fragment between the iliac wings.

4. Mally, quoted by Foix and Hillemand.<sup>13</sup>

5. Friedel, G.: Defekt der Wirbelsäule vom 10. Brustwirbel an abwärts bei einen Neugeborenen, *Arch. f. klin. Chir.* **93**:944, 1910.

6. Fitch, R. R.: Congenital Absence of Vertebrae Below First Sacral, *Am. J. Ortho. Surg.* **7**:540, 1910.

7. White, C.: A Fetus with Congenital Absence of the Sacrum, *Proc. Roy. Soc. Med.* **4**:279, 1911.

8. Charlier and Sauty: Spina bifida géant, *Rev. d'orthop.* **4**:257, 1913.

9. Rendu, A., and Verrier, H.: Absence partielle du sacrum, malformations multiples, *Rev. d'orthop.* **4**:311, 1913.

Bradburn<sup>10</sup> reported the case of a man, aged 24, who had been incontinent since birth. His feet were contracted and the sacrum and coccyx were almost entirely missing.

Stewart's<sup>11</sup> patient was an incontinent boy, aged 6 years, who was very active on his feet, which were in the equinovarus position. The sacrum and coccyx were missing.

Desfosses and Mouchet<sup>12</sup> reported the case of an incontinent girl, aged 7½ years, whose feet were in the equinovarus position. The rectum opened into the vagina; the lower two lumbar vertebrae, the sacrum and coccyx were missing.

Foix and Hillemand<sup>13</sup> reported the case of a man, aged 51, who had been incontinent until the age of 14, although there was subsequent slight improvement. There was atrophy of the buttocks, thighs and feet. The fifth lumbar vertebra was sacralized. The four sacral segments and the coccyx were missing.

The patient of Foix, Hillemand, Achard and Mozon<sup>14</sup> was an incontinent woman, aged 21, with atrophy of the buttocks. The intergluteal groove was almost absent, and the fifth lumbar vertebra was sacralized. The lower three sacral segments and the coccyx were absent.

Leri and Linossier<sup>15</sup> reported the case of an incontinent woman, aged 41, who had had two full term pregnancies, both children dying during the delivery. The right foot was in the equinovarus and the left in a laterally displaced position. The lumbar portion of the spine was deformed and fused, and the sacrum and coccyx were absent.

Drehmann's<sup>16</sup> patient was an incontinent boy, aged 1 year, who had club feet and a weak musculature of the lower extremities. The last two lumbar vertebrae and the sacrum and coccyx were missing.

Brack's<sup>17</sup> patient, a stillborn child, had a deformity resembling a sirene and was of undetermined sex. The sacrum and coccyx were missing.

---

10. Bradburn, W. R.: Interesting Case of Infected Bladder and Kidneys Due to Malformation of Sacrum, *New Orleans M. & S. J.* **74**:633 (March) 1922.

11. Stewart, S. F.: Absence of Sacrum, *Arch. Surg.* **9**:647 (Nov.) 1924.

12. Desfosses, P., and Mouchet: Absence du sacrum, *Rev. d'orthop.* **11**:61, 1924.

13. Foix, C., and Hillemand, P.: *Dystrophie cruro-vesico-fessière*, *Rev. neurol.* **31**:450, 1924.

14. Foix: Hillemand; Achard and Mozon, cited by Foix and Hillemand.<sup>13</sup>

15. Leri, A., and Linossier: Absence du sacrum, *Bull. et mém. Soc. méd. d. hôp. de Paris* **49**:504 (March 27) 1925.

16. Drehmann, G.: Ueber angeborene Wirbeldefekte, *Beitr. z. klin. Chir.* **139**: 191, 1927.

17. Brack, E.: Ueber das Kreuzbein, *Virchows Arch. f. path. Anat.* **272**:295, 1929.



Feller and Sternberg's<sup>18</sup> patient was a premature stillborn girl. Atresia of the rectum was present. The feet were in the equinovarus position, and the abdominal organs were normal. The lower four lumbar segments and the sacrum and coccyx were missing.

#### REPORT OF CASES

The two cases from this clinic follow.

CASE 1.—S. J., aged 14 months, had had deformities of the spine and legs since birth. She was born at full term of a 20 year old primipara by normal delivery. At birth shortening of the thighs and torso was noted. Loss of tone of the bowel



Fig. 1 (case 1).—The patient at the age of 14 months. Note the lumbar kyphosis, the atrophy of the buttocks and the equinovarus deformity of the feet.

and bladder sphincters was soon evident. The family history was essentially unimportant. Physical examination revealed the following positive findings:

1. A short torso with lumbar kyphosis.
2. Dislocation of the hip joints.
3. Flexion contractures of the knees of 20 degrees.
4. Bilateral talipes equinovarus.
5. Fecal and urinary incontinence.
6. Flattening of the buttocks and some atrophy of the thighs posteriorly.

Roentgen examination showed the following significant features:

1. Partial or complete fusion of the ribs on both sides of the thorax.
2. Spina bifida occulta of the upper dorsal region.
3. A right lumbar rib.
4. Three rudimentary lumbar vertebrae.
5. Loss of osseous continuity between the third lumbar vertebra and the pelvis.

18. Feller, A., and Sternberg, H.: Zur Kenntnis der Fehlbildungen der Wirbelsäule, *Virchows Arch. f. path. Anat.* 280:649, 1931.

6. Absence of the sacrum and coccyx, the iliac wings almost touching posteriorly.
7. Bilateral dislocation of the hip joints.

The patient's parents were advised to return with the child when she was 2 years old for correction of the deformities of the knees and feet. At that time the child was able to sit alone and to stand by bracing the knees against each other. Operative correction was again advised, but the patient did not return for treatment.



Fig. 2 (case 1).—Roentgenogram showing absence of the sacrum and of the lower two lumbar vertebrae, deformities of the thorax and dislocated hips.

CASE 2.—R. S., aged 9 years, was unable to bend the knees or to walk without crutches. There was backward bending of the left knee with turning out of the legs. The deformities mentioned were present at birth, which was normal. Urinary and fecal incontinence was complete, but intestinal control improved gradually. At the age of 5 years, following closed reduction of the hips (?) and femoral osteotomies to correct severe internal rotation contractures, the patient was able to walk. However, the position of the leg gradually changed to a progressive external rotation contracture and a left "back-knee." Crutches became necessary.

Physical examination showed the following positive findings:

1. Bilateral valgus of the feet, with marked contractures of the achilles tendon.
2. The right knee in full extension and allowing only a few degrees of flexion.
3. The left knee in 50 degrees of recurvation, flexion being blocked by the contracted quadriceps.
4. Dislocation of the hip joints with outward rotation contractures and limitation of hip motion in flexion and internal rotation.
5. Urinary incontinence.
6. Rudimentary but descended testicles.
7. Atrophy of the thighs and buttocks with short intergluteal fold.

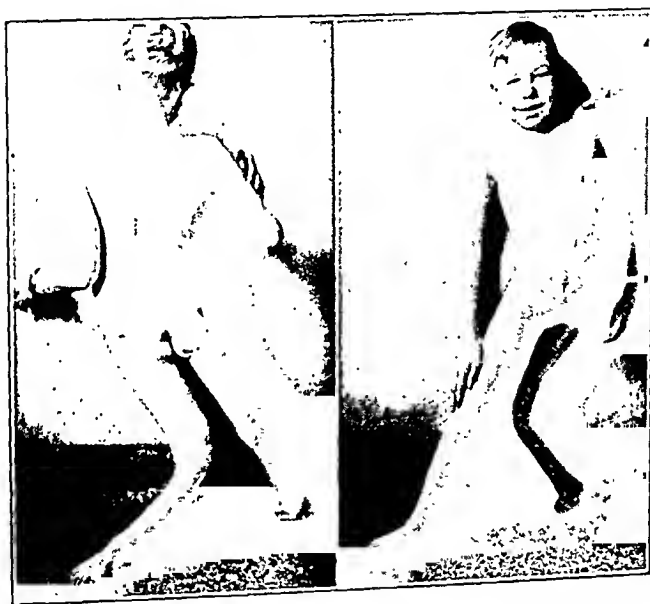


Fig. 3 (case 2).—The patient at the age of 9 years. Note the atrophy of the buttocks and thighs, the perineal disturbance and the deformities of the lower extremities.

Roentgen examination showed the following significant features:

1. Four lumbar vertebrae.
2. Absence of the sacrum and coccyx, with the iliac wings in close apposition posteriorly.
3. Dislocation of the hip joints.
4. Small knee joints, with normal contours.

Following a Bennett plastic lengthening of the left quadriceps muscle, full extension of the knee was obtained, which was later improved by means of turn-buckle casts to allow 15 degrees of flexion. The patient became ambulatory in the long leg braces and with crutches. Later supracondylar femoral osteotomies corrected the external rotation contractures, and the patient was able to walk with good alinement of the lower extremities.



Fig. 4 (case 2).—The patient one year after the last operation.



Fig. 5 (case 2).—Roentgenogram showing absence of the sacrum, the presence of four lumbar vertebrae and dislocated hips.

## COMMENT

From the eighteen cases reported in the literature and the two reported in this article, it is noted that absence of the sacrum is often compatible with life and that associated with the primary defect of the vertebral spine are characteristic clinical findings which are due in part to the deformity itself and in part to the accompanying lesion of the nervous system. The manifestations of the deformity itself are a characteristic flattening of the contour of the caudal region, absence of the buttock prominences and the groove between them, absence of sacral spinous processes and on rectal examination the encountering of soft tissue instead of the normal bony concavity of the sacrococcygeal segments. The iliac wings appear pushed together posteriorly and are almost vertical, thus narrowing the pelvic canal. Very characteristic are the roentgenologic findings which remove any doubts which are present after a clinical examination.

With the typical neurologic and orthopedic manifestations are primarily associated incontinence of urine and occasionally incontinence of feces as well. This incontinence is complete but may show slight improvement in later years, especially during the day time. It is of interest that despite the urinary difficulty the genital system usually escapes involvement, as demonstrated by the ability of two adult females to carry their progeny to term. Leri and Linossier explained this on the basis of loss of innervation to the urinary organs, which is sacral in origin, as compared with the genital innervation, which is lumbar.

Next in frequency are the deformities of the feet, which were absent in only six cases. As a rule, the deformity is a paralytic club-foot, in some cases one foot being in the equinovarus and the other in the calcaneovalgus position. There can be no doubt that these deformities of the feet are due to a lesion of the sacral or lumbosacral plexus, as they occur also in cases of spina bifida occulta and spina bifida aperta. As far as the sensory disturbance is concerned, it is difficult to obtain a clear picture from the data in the literature. In some cases the patient is reported as having complete sensory and motor loss of the lower extremities, while in other cases with apparently the same degree of involvement the nervous disturbance did not seem to be pronounced. These differences may be due in great part to the amount of care taken during the neurologic examination. More accurate examination reveals the sensory and motor loss to be that of the sacral or lower lumbosacral plexus.

Foix and Hillemand were impressed by the clinical similarity of the cases with congenital absence of the sacrum. They considered the clinical picture to be a syndrome for which they introduced the term *dystrophie*

*cruro-vesico-fessière* and emphasized especially the characteristic atrophy of the gluteal regions. This term is not descriptive from the pathologic point of view, because there is no real dystrophy, as all the symptoms included in the term are entirely due to the myelodysplasia or congenital lesion of the plexus connected with absence of the sacrum. From the clinical point of view, however, the term may be acceptable, as it includes the outstanding clinical symptoms, namely, involvement of the lower extremities, the bladder and the gluteal regions.

To the group of infrequent findings belongs the dislocation of the hip joint, which was present bilaterally in four cases. The severe pelvic deformity with almost vertical iliac wings doubtless represents the mechanical reason for the deformity.

In ten cases associated anomalies of the vertebral spine were found in more cranial segments, most frequently in the lumbar region. This shows clearly that there is only a gradual but not an essential difference in the deformities of the spine.

Absence of the sacrum is also of practical interest to the obstetrician. Albrecht introduced the term "dyspygic pelvis" for this pelvic deformity, which is characterized by a marked decrease in the transverse diameter. Litzmann stated the belief that it is a third type of pelvis with a narrow transverse diameter and classified it with the ankylotic and the kyphotic pelvis. That the female with this type of pelvis is handicapped is evidenced by the difficulties during labor which are mentioned in the case of Litzmann and in that of Leri and Linossier.

As far as etiology is concerned, there is no doubt that the condition must date, as do all severe congenital deformities of the spine, to the early days of embryonal life. Several theories have been advanced, varying from Wertheim's theory of late prenatal origin to Friedel's conception of a minute embryonal trauma producing a longitudinal kink in the long embryonal axis, with caudal suppression. The most plausible theory is the hypothesis of Feller and Sternberg, which explains the sacral variations and peripheral manifestations on the basis of a varying degree of defects in the posterior portions of the metameric segments, with additional involvement of the anterior portions in cases with abdominal visceral anomalies. They advanced their theory in contrast to Bolk's theory of complete suppression of the segments. The latter author was unable to explain a complete segmental defect in the vertebral spine with normal development of the ventral organs.

The treatment can be only symptomatic. Simple orthopedic procedures, such as manipulative correction of the deformities of the lower extremities for young children and osteotomies for older persons, can be of great benefit, as shown in one of our cases.

## SUMMARY

To the eighteen cases of absence of the major part or all of the sacrum and coccyx reported in the literature two cases were added, both with complete absence of the sacrum and coccyx.

The associated findings which predispose to this diagnosis are urinary incontinence, clubfoot, absence of the coccyx and of all or part of the sacrum, occasional sacralization of the last lumbar vertebra and atrophy of the buttocks and thighs.

Treatment is directed toward correction of the deformity of the lower extremity if sufficiently active muscular action is present to indicate that the patient will be able to assume the erect position when the lower extremities and the spine are alined.

# EFFECT OF PNEUMOTHORAX AND OLEOTHORAX ON THE HISTOLOGIC STRUCTURE OF THE THYROID GLAND

A. CLIFFORD ABBOTT, M.D., F.R.C.S. (Edin.)

ALEXANDER M. GOODWIN, M.D.

SARA MELTZER, M.D.

AND

EARL STEPHENSON, M.D., C.M.

WINNIPEG, CANADA

Celsus,<sup>1</sup> discussing the study of anatomy by the dissection of living criminals, a practice in vogue in Alexandria in the third century B. C., stated:

It is indeed true that the abdomen, with which our argument is less concerned, can be opened while a man yet lives, but as soon as the knife reaches the thorax, and cuts the transverse septum, which is a membrane dividing the superior parts from the inferior and called diaphragma by the Greeks, the man at once gives up the ghost and thus it is the breast and its viscera of a dead man and not a living man which the murderous physician examines. He had thus performed a cruel murder and has not learned what the viscera of a living man are like.

In this article we are not concerned with the results of opening the thoracic cavity. We are, however, interested in what effect a large pneumothorax has on the thyroid gland, and we wish to raise the question of whether pneumothorax produces anoxemia. The problem, although physiologic, has received scant attention. To the clinician it is of prime importance to know in what way he alters the physiology of respiration and what changes he causes in other organs when he produces pneumothorax in a patient. To the thoracic surgeon also it is essential to know the gross effects of pneumothorax.

Marine, Spence and Cipra,<sup>2</sup> Webster and Cipra,<sup>3</sup> Baumann, Cipra and Marine<sup>4</sup> and Chesney, Clawson and Webster<sup>5</sup> have shown that an

---

From the Departments of Physiology and Pathology, the University of Manitoba.

This work was made possible by a grant from the Banting Research Foundation.

1. Celsus, quoted by Wells, H. G.: *Outline of History*, New York, The Macmillan Company, 1920, vol. 1, p. 403.

2. Marine, D.; Spence, A. W., and Cipra, A.: *Proc. Soc. Exper. Biol. & Med.* **29**:822 (April) 1932.

3. Webster, D., and Cipra, A.: *Proc. Soc. Exper. Biol. & Med.* **27**:1026 (June) 1930.

4. Baumann, E. J.; Cipra, A., and Marine, D.: *Proc. Soc. Exper. Biol. & Med.* **28**:1017, 1931.

5. Chesney, A. M.; Clawson, I. A., and Webster B.: *Bull. Johns Hopkins Hosp.* **43**:261 (Nov.) 1928.



exclusive diet of cabbage produces a large hyperplastic goiter in rabbits. They have also proved that it is the cyanide content that produces this change. Their work has been confirmed and elaborated by McCarrison, Sankaran and Madhava.<sup>6</sup> Marine expressed the belief that the effect on the rabbits was due to anoxemia. It is an old, established physiologic

TABLE 1.—Results of Pneumothorax on Puppies\*

	Animal No.	Duration of Compression	Amount of Air Introduced, Cc.	More Colloid	More Colloid Doubtful	No Change	Hyperplasia and Infection	Effusion and Necrosis	Section Lost
1 week									
	244	9 days	80	..	..	..	..	+	..
	242	7 days	90	..	..	..	..	+	..
	241	7 days	90	..	..	+	..	..	..
Total	3					1		2	
2 weeks									
	243	13 days	100	..	..	+	..	..	..
	182	13 days	55	..	..	+	..	..	..
	181	13 days	60	..	..	+	..	..	..
	172†	12 days	785	..	..	..	+	..	..
	171†	12 days	774	..	..	+	..	..	..
	161	17 days	50	..	..	..	..	..	..
	158	16 days	30	..	..	..	..	+	..
	133	13 days	45	..	..	+	..	..	..
	130	14 days	45	..	..	..	..	+	..
	128	15 days	60	..	..	..	..	+	..
	126	12 days	60	..	..	..	..	+	..
	124	15 days	60	..	..	..	..	+	..
	122	11 days	60	+	..	..	..	..	..
	121	12 days	60	+	..	..	..	..	..
	120	12 days	60	+	..	..	..	..	..
Total	15			3		5	1	5	1
3 weeks									
	183	19 days	55	..	..	+	..	..	..
	159	21 days	15	..	..	+	..	..	..
	181	21 days	40	..	..	+	..	..	..
	123	19 days	60	+	..	..	..	..	..
	125	22 days	60	+	..	..	..	..	..
Total	5			2		3			
Long duration									
	129	82 days	45	..	..	+	..	..	..
	127	82 days	10	..	..	+	..	..	..
Total	2					2			

\* The result obtained in each instance is indicated by +.

† This was a very large puppy.

fact <sup>7</sup> that cyanides produce internal anoxemia; that is, they inhibit individual cellular respiration. In recent years the contention has been that all patients with hyperfunctioning thyroid glands are anoxemic, and oxygen tents have been used with good results in thyroid crises, both preoperatively and postoperatively.

6. McCarrison, R.; Sankaran, G., and Madhava, K. B.: *Indian J. M. Research* 20:723 (Jan.) 1933.

7. Sollmann, T.: *Manual of Pharmacology*, ed. 3, Philadelphia, W. B. Saunders Company, 1926, p. 773.

Reich and Blauel<sup>8</sup> showed that tracheal stenosis produced colloid goiter. This work was confirmed by Breitner.<sup>9</sup> Both groups believed the change to be due to a lack of oxygen, presumably anoxemia of the external type. In a recent publication<sup>10</sup> we confirmed the fact that tracheal stenosis, if severe enough, produces a colloid, quiescent phase in the thyroid gland. At the same time we raised the question as to whether this change is due to anoxemia, to partial asphyxia or to some much more complicated biochemical process. During the course of our experiments on tracheal compression, the question arose as to whether a large pneumothorax or an oleothorax would not produce the same effect. It is with this that we shall now deal.

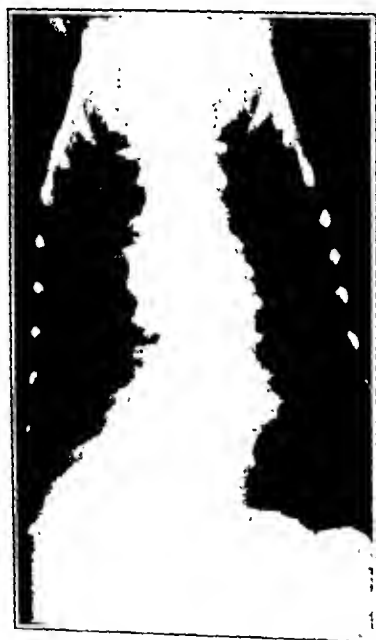


Fig. 1.—A roentgenogram showing pneumothorax in a dog with 175 cc. of air in each pleural cavity; this is equal to 30 cc. per pound of body weight.

In this work all the animals were housed and fed in the same way and the same technic was used as in our work on tracheal compression.<sup>10</sup> All oleothoraxes and pneumothoraxes were effected with strict anti-septic and aseptic precautions. We considered it necessary in these experiments to use large compressions. Experimentally, we found that the animals would tolerate, without showing marked evidence of embarrassment, about 30 cc. of air or oil per pound (0.45 Kg.) of body weight equally divided between the two sides. This amount was used

8. Reich and Blauel: Beitr. z. klin. Chir. 82:475, 1912-1913.

9. Breitner: Acta chir. Scandinav. 57:207, 1924.

10. Abbott, A. C.; Goodwin, A. M., and Meltzer, S.: Canad. M. A. J. 28: 481, 1933.

in all animals except those specially marked in tables 1 and 2; those few received less. Figure 1 is a roentgenogram of a dog with a bilateral pneumothorax in which we used 30 cc. of air to the pound of body weight. In the majority of animals we used oil instead of air, as no refilling was required. Sections from the thyroid gland were taken before a compression was done and at the end of the experiment, for comparison.

In our first series twenty-six puppies were used. In all except two, 30 cc. of oil per pound of body weight was used for compression. In the great majority of the animals we used olive oil sterilized by simple boiling. As shown in table 1, in seven animals there developed an effusion in the pleural cavity associated with necrosis of the thyroid gland. The two conditions appeared to go hand in hand. In none of



Fig. 2.—*A*, a roentgenogram showing iodized poppy-seed oil injected into the trachea of a normal dog. (Note its penetration to the periphery of the lung.) *B*, a roentgenogram showing massive compression of the same lung by the injection of 30 cc. of air per pound of body weight. This caused little distress in the dogs. Note the poppy-seed oil extending to the very periphery of the lung.

the animals in which the lungs were compressed for a period of one week did the thyroid gland revert to the colloid state. In three animals the thyroid gland reverted to a more colloid state after two weeks of compression; in five it showed no change; in one there developed hyperplasia associated with an infection, and in five there was necrosis associated with an effusion. The lungs of five animals were compressed for a period of three weeks; in two the thyroid gland became more colloid, and in three it showed no change.

We were interested to know what part of the lung was compressed most by pneumothorax. Figure 2 *A* is a roentgenogram of a dog taken after the intratracheal injection of iodized poppy-seed oil 40 per cent. Thirty cubic centimeters of air per pound of body weight was then

injected into the pleural cavities and another roentgenogram was made (fig. 2 *B*). It will be noted that the iodized poppy-seed oil penetrated almost completely to the periphery of the lung. This was true in several dogs. The process was then reversed. In several dogs pneumothorax was secured with 30 cc. of air per pound of body weight. Iodized poppy-seed oil was then injected as before (the roentgenograms in figure 3 *A* and *B* show the results in two dogs). In no case did the iodized poppy-seed oil penetrate to the periphery. It appears, therefore, that it is the terminal portion of the bronchial tree which is collapsed most by pneumothorax.

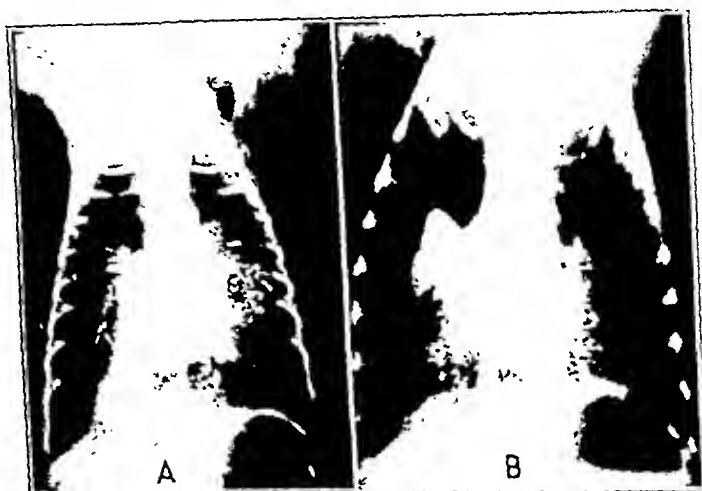


Fig. 3.—In this animal a bilateral collapse was effected before poppy-seed oil was injected. In *A*, note the failure of the poppy-seed oil to penetrate to the periphery of the lung. This indicates that the terminal bronchioles are compressed and possibly obliterated in massive pneumothorax. *B*, also shows the failure of the poppy-seed oil to penetrate to the periphery.

TABLE 2.—Results of Pneumothorax in Adult Dogs and a Cat

Animal No.	Duration of Compression	Amount of Air Introduced, Cc.	More Colloid	More Colloid Doubtful	No Change	Hyperplasia and Infection	Effusion and Necrosis	Section Lost
10	14 to 21 days	30	0	0	10	0	0	0

In two dogs the compression was allowed to persist for eighty-two days; no change in the thyroid gland was found.

Next we used ten adult dogs and one adult cat. Compression was accomplished by using 30 cc. of liquid petrolatum per pound of body weight. The oil was sterilized by boiling. In none of the animals did pleural effusion occur. We are of the opinion that olive oil must be sterilized at a constant temperature to avoid the production of effusion. In none of the animals was there a change in the thyroid gland (table 2).

Our next series consisted of twenty-six kittens. As we have already shown,<sup>10</sup> the thyroid glands of these animals are more hyperplastic than are those of puppies. In seventeen animals oleothorax was produced (30 cc. of oil per pound of body weight), and this was maintained for one week. At the end of that period the thyroid glands of four animals showed more colloid content, and that of another probably contained more colloid. In eight there was no change in the gland, and in four, either the first or the second section was lost, making comparison impossible.

The lungs of nine kittens were compressed for a period of two weeks. The results in these animals were much more positive. In six the thyroid gland showed definite reversion to a colloid type and one was doubtfully colloid. One showed no change, and in one the section was lost. It will therefore be noted that in seven of eight kittens, compression of the lungs appeared to produce a deposit of colloid in the thyroid.

#### COMMENT

In carrying out the work we observed that these animals tended to lose weight in spite of the fact that they were less active. The fact that they were less active automatically produces a lessened metabolism and a storage of colloid. On the other hand, the respiratory rate was definitely increased, which means an increase in the energy expended, an increase in the metabolism and a consequent decrease in the colloid. It is possible that these two factors counterbalance one another.

As in our experiments on tracheal compression,<sup>10</sup> adult animals showed no response, the thyroid being naturally colloid and very stable. Nine of the puppies were ruled out on account of effusions, infection and lost sections. Of the sixteen remaining animals, the thyroid glands of approximately 33 per cent showed a deposition of an increased amount of colloid. This is only suggestive.

In kittens, which we have already shown to be more susceptible to stimuli,<sup>10</sup> the results were more positive. Figure 4 is a photomicrograph showing the change in the texture of the thyroid after compression of the lungs by oleothorax. The lungs of seventeen animals were compressed for one week. Four of these animals were eliminated from consideration owing to the loss of sections. Of the remaining thirteen, in five the thyroid gland became more colloid after compression of the lung. In animals the lungs of which were compressed for two weeks, however, seven of eight for which the results are acceptable showed colloid reversion of the thyroid.

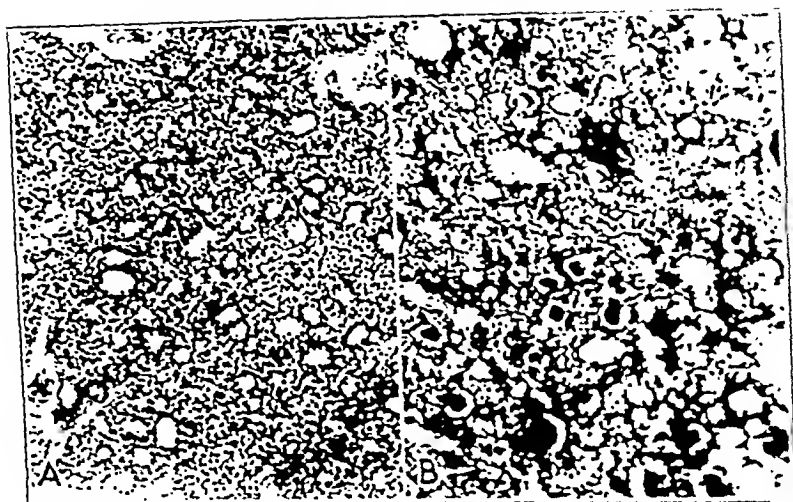


Fig. 4.—*A*, a photomicrograph of the thyroid gland of a kitten before oleo-thorax. *B*, a photomicrograph of the same thyroid gland two weeks after compression. Note the increase in the number of acini filled with colloid and also the increase in the size of the acini.

TABLE 3.—*Results of Pneumothorax on Kittens\**

	Animal No.	Duration of Compression	Amount of Air Introduced, Cc.	More Colloid	Probably More Colloid	No Change	Hyper-plasia and Infection	Section Lost
1 week								
	198	7 days	10	÷	..	..	..	..
	192	7 days	20	..	..	..	..	..
	191	7 days	20	..	..	..	..	..
	190	7 days	20	..	..	..	..	..
	189	7 days	20	..	..	..	..	..
	188	7 days	20	..	..	..	..	..
	186	8 days	20	..	..	+	..	..
	185	8 days	20	..	..	+	..	..
	177	8 days	50	..	..	..	..	..
	180	8 days	40	+	..	..	..	..
	179	8 days	50	..	..	..	..	..
	178	5 days	50	+	..	..	..	+
	149	8 days	40	..	..	..	..	..
	231	7 days	25	..	..	..	..	÷
	230	7 days	35	..	..	+	..	..
	224	3 days	10	..	..	..	..	..
	223	8 days	10	..	..	..	..	+
Total	17			4	1	8	..	4
2 weeks								
	199	13 days	15	÷	..	..	..	..
	197	13 days	5	+	..	..	..	..
	195	13 days	10	..	..	+	..	..
	194	13 days	10	÷	..	..	..	..
	193	15 days	5	..	÷	..	..	..
	163	14 days	15	..	..	..	..	..
	214	14 days	100	+	..	..	..	+
	184	14 days	50	÷	..	..	..	..
	200	13 days	20	÷	..	..	..	..
Total	9			6	1	1	..	1

\* The result obtained in each instance is indicated by ÷.

## SUMMARY

Pneumothorax or oleothorax was produced in sixty-four animals.

It appears that the periphery of the lung is compressed to a greater extent by these procedures.

Pneumothorax and oleothorax have no apparent effect on the thyroid gland of adult animals.

Pleural effusions in our experimental animals were practically always associated with necrosis of the thyroid epithelium.

In puppies, compression of the lung produced reversion to the colloid state in the thyroid in 31.2 per cent. of the animals.

In kittens the same degree of compression based on body weight produced reversion of the thyroid to the colloid state in 57.1 per cent. In eight kittens the lungs were compressed for two weeks, and the percentage showing colloid reversion of the thyroid rose to 87.4.

# PRIMARY SARCOMA OF THE DUODENUM

REPORT OF A CASE

DUVAL PREY, M.D.

JOHN M. FOSTER JR., M.D.

AND

WILFRED DENNIS, M.D.

DENVER

Primary sarcoma of the duodenum is an extremely rare disease, as evidenced by the fact that a careful review of the literature reveals only sixty-one authentic cases. That further study of this infrequent condition may be encouraged, we have collected data on all of the cases previously described and have added the observations on one of our own.

Only cases in which it was definitely stated that the tumor was of the duodenum were considered; although numerous sarcomas of the small intestine have been reported, the authors unfortunately failed to mention the exact location of the growth. Cases in which a metastatic involvement of the duodenum was present were not considered; cases of this sort are not so infrequent as one might think.

Sarcoma of the duodenum, like sarcoma elsewhere in the intestinal tract, is most commonly of the round cell variety, although spindle cell sarcoma, myosarcoma and melanosarcoma have occurred. In contradistinction to carcinoma, sarcoma of the intestine originates in the submucosa or muscularis and grows longitudinally, infiltrating the intestinal wall to such an extent that it is transformed into a rigid, nonyielding tube. Surprisingly, the lumen is encroached on rarely to a degree sufficient to cause obstruction. For this reason it is uncommon to find obstructive symptoms before the tumor attains an enormous size. Sarcomas do not show areas of ulceration so rapidly as do carcinomas. Unlike carcinoma, sarcoma of the duodenum is encountered almost as frequently in women as in men, and the persons afflicted are much younger.

Sarcomas grow to an enormous size; the average weight reported in the literature for these growths in the duodenum is 500 Gm. The gross appearance is usually that of a smooth, gray, cylindric mass, beginning and ending rather abruptly and covered by normal serosa. However, the tumor may consist of a polypoid mass extending into the lumen of the bowel. This form, although common in other portions of the intestinal tract, is extremely rare in the duodenum.

---

From the Surgical Service of the Denver General Hospital.



In 1877 Alexander reported the first case of sarcoma of the duodenum. In addition to this case we have been able to collect sixty-one

*Cases of Sarcoma of the Duodenum in the Literature*

Case	Author*	Sex	Age, Years	Classification
1	Albon.....	..	..	Lymphosarcoma
2	Alexander.....	M	18	Lymphosarcoma
3	Bier.....	..	..	.....
4	Brandt.....	M	23	Lymphosarcoma
5	Cavazzani.....	..	..	.....
6	Crowther.....	F	25	.....
7	Davld.....	..	..	.....
8	Duval.....	M	44	Melanosarcoma
9	Elger.....	M	25	Lymphosarcoma
10	Elger.....	F	33	Lymphosarcoma
11	Feldman.....	F	48	Lymphosarcoma
12	Feldman.....	F	27	.....
13	Flexner.....	M	27	Lymphosarcoma
14	Flexner.....	F	11	Lymphosarcoma
15	Foxwell.....	F	28	Myxosarcoma
16	Freud.....	F	50	Lymphosarcoma
17	Freud.....	F	22	Lymphosarcoma
18	Freud.....	M	34	Lymphosarcoma
19	Gerster.....	M	..	.....
20	Ghon and Hiltz.....	M	81	Myosarcoma
21	Ghon and Roman.....	M	25	Lymphosarcoma
22	Ghon and Roman.....	F	49	Lymphosarcoma
23	Hammer.....	M	40	Lymphosarcoma
24	Hndel.....	M	32	Melanosarcoma
25	Illoway.....	M	40	Lymphosarcoma
26	Kathe.....	M	57	Myosarcoma
27	Latzel.....	..	..	Lymphosarcoma
28	Libman.....	M	12	Lymphosarcoma
29	Libman.....	M	35	Lymphosarcoma
30	MneKenzie.....	M	18	Lymphosarcoma
31	Mandelbaum and Libman.....	..	..	Lymphosarcoma
32	Mayer.....	F	36	Lymphosarcoma
33	Miller, C. J.....	F	73	Lymphosarcoma
34	Moore.....	F	41	Lymphosarcoma
35	Mostowska.....	..	..	Lymphosarcoma
36	Perry and Shnw.....	M	63	.....
37	Perry and Shaw.....	M	38	Lymphosarcoma
38	Perry and Shaw.....	F	30	Lymphosarcoma
39	Petrow.....	M	34	Lymphosarcoma
40	Ffundt.....	F	41	Spindle cell sarcoma
41	Rademneher.....	M	40	Spindle cell sarcoma
42	Ralford.....	F	42	Lymphosarcoma
43	Renner.....	F	15	Lymphosarcoma
44	Robb.....	F	59	Spindle cell sarcoma
45	Robb.....	F	23	Melanoma sarcoma
46	Rolleston.....	F	30	Lymphosarcoma
47	von Salis.....	M	40	Myosarcoma
48	Schnpiro.....	M	23	Spindle cell sarcoma
49	Schmidt.....	M	57	Lymphosarcoma
50	Shifflett.....	F	48	Spindle cell sarcoma
51	Soli.....	..	..	.....
52	Strnuss, Block, Fried and Hamburger.....	M	62	Lymphosarcoma
53	Storch.....	M	25	Lymphosarcoma
54	Verehely.....	..	..	.....
55	Verehely.....	..	..	.....
56	Verehely.....	..	..	.....
57	Valdes.....	F	11	.....
58	Vonwyl.....	F	74	.....
59	Weeden.....	F	34	Lymphosarcoma
60	Wesener.....	M	55	Myosarcoma
61	Wolfram.....	F	..	.....

\* Exact references for these reports will be found in the bibliography.

other cases and to classify a large percentage of them as to the age and sex of the patient and the type of growth, despite the many difficulties encountered because of the incompleteness of the records (table).

Contrary to the general belief that malignant conditions of the duodenum are seen more commonly in men than in women, sarcomas of the

duodenum were found to be about evenly divided between the sexes. In the fifty cases in the report of which the sex was stated, twenty-six of the patients were male, and twenty-four, female. It is clearly demonstrated even in such a small series that the sex of the patient is of little value as an aid to the diagnosis of this condition.

It is accepted that in younger persons sarcoma occurs more frequently than does carcinoma, and this is emphasized most strikingly by the cases of duodenal sarcoma. In forty-eight instances the age was mentioned, and the average was 38 years. This is considerably less than the average age in a similar series of cases of carcinoma. The oldest patient in the group was 81 years of age, while the youngest patients were two girls, each 11 years old. Interestingly, only five sarcomas of the duodenum have occurred in patients over 60, while eighteen, or approximately one third of the total number reported, have occurred in patients under 25.

In only forty-seven reports was the histologic picture described sufficiently for the proper classification of the type of sarcoma. As expected, lymphosarcoma was most frequently encountered, occurring thirty-five times, while spindle cell sarcoma occurred five times, myosarcoma four times, melanosarcoma three times, and myxosarcoma once.

In the case that we shall report the growth belonged to the most common group, namely, primary lymphosarcomas of the duodenum.

#### REPORT OF CASE

*History.*—J. G., aged 48, a laborer, was admitted to the Denver General Hospital on March 13, 1933, with persistent and progressive nausea and vomiting of three and one-half months' duration. The vomiting had increased until at the time of admission he vomited practically everything that was eaten. Previous to three and one-half months before entrance he had no symptoms of gastrointestinal derangement and considered himself to be in perfect health. One month prior to his entry to the hospital he became conscious of a mass in the upper part of the abdomen, which was not tender and from which he suffered no discomfort. He had lost 20 pounds (9.1 Kg.) in weight during this period and had noticed a marked decrease in strength. There had never been any hematemesis or jaundice. There had been varying degrees of constipation but no diarrhea. The stools were light yellow; they had never been tarry. There was nothing in the patient's history or the family history which had any bearing on the illness.

*Examination.*—The patient was an anemic and undernourished man, aged 48 years. The skin appeared sallow; it was cold and moist, but there was no evidence of an icteric tinge. The pulse rate was 100, and the blood pressure was 110 systolic and 80 diastolic; the temperature was 99 F. Oral examination showed caries of the teeth and embedded tonsils. The heart was of normal size; the sounds were of good quality and there were no murmurs. Examination of the lungs revealed no obvious pathologic condition. The abdomen was scaphoid and soft and contained a palpable mass above the umbilicus which extended into the right upper quadrant. This mass was hard, smooth and slightly movable and



Fig. 1.—Roentgenogram of a sarcoma of the duodenum, demonstrating the deformity of the greater curvature of the stomach and the dilatation of the first portion of the duodenum as a result of the pressure by the tumor.



Fig. 2.—Roentgenogram revealing a residue of the barium meal in the stomach with a small amount of the opaque medium distributed through the alimentary tract.

appeared to be about the size of a grapefruit. The pulsations of the aorta were transmitted through this mass. The liver and spleen were not palpable. The extremities were normal.



Fig. 3.—Macroscopic view of the specimen, showing a portion of the stomach and duodenum above the tumor. Part of the pancreas, as well as the normal jejunum, can be seen.



Fig. 4.—Macroscopic view of the opened specimen. The arrows point to the beginning and the end of the tumor.

The blood count was as follows: hemoglobin, 70 per cent; erythrocytes, 3,250,000 per cubic centimeter, and leukocytes, 13,400, consisting of 26 per cent lymphocytes and 74 per cent polymorphonuclears.

The Wassermann reaction was negative, and chemical examination of the blood revealed: sugar, 80 mg. per hundred cubic centimeters; nonprotein nitrogen, 40 mg.; urea nitrogen, 17 mg.; creatinine, 1.07 mg., and chlorides, 350 mg.

Analysis of the gastric juice showed that there was no free hydrochloric acid; the total acidity was 5, and the contents showed lactic acid and Boas-Oppler's bacilli. Roentgen examination after a barium sulphate meal showed that the stomach was well filled, with the greater curvature pushed upward from below by a rounded mass (fig. 1). The pylorus was normal, and the duodenal cap was dilated to many times its normal size, apparently as a result of an obstruction

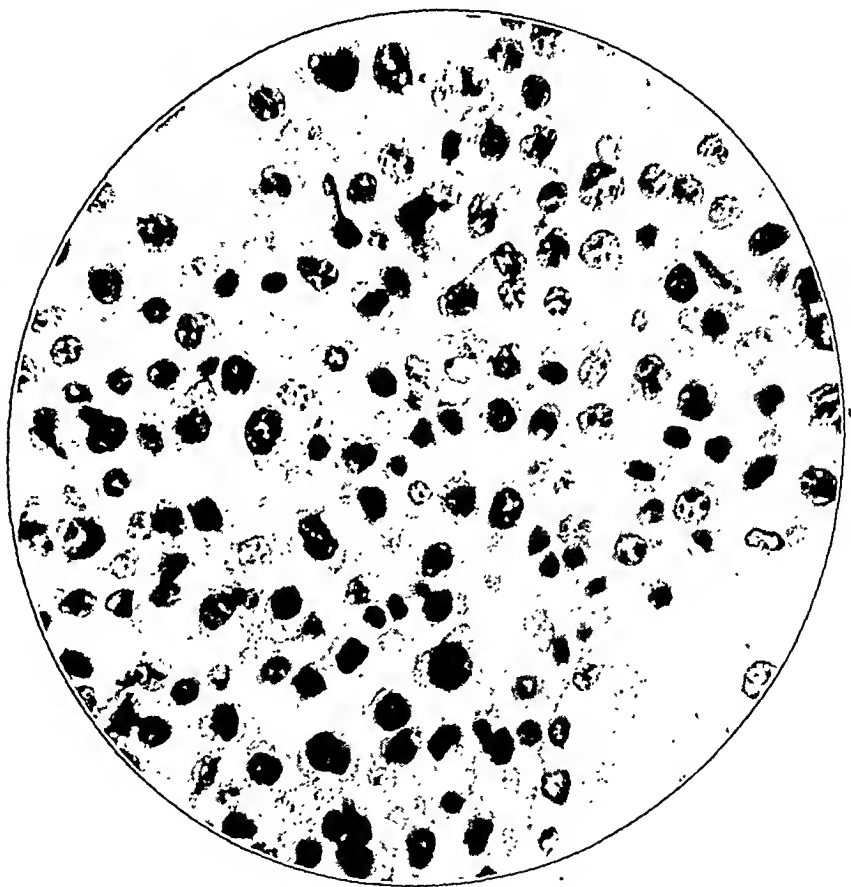


Fig. 5.—Microscopic section of the tumor, showing round cells of fairly uniform size, occasional giant cells and many mitotic figures.

in the second portion of the duodenum. The six hour examination (fig. 2) revealed a slight residue of the barium meal in the stomach, with small amounts of the opaque medium distributed through the alimentary tract.

*Operation and Course.*—On March 17, 1933, operation was performed by one of us (D. P.), which disclosed a hard tumor involving the second and third portions of the duodenum, slightly movable and about the size of a large grapefruit. The mass was grayish and cylindric and ended abruptly at the duodenojejunal juncture. The mass could not be freed from the pancreas posteriorly, and because of its size and situation it was irremovable. There was some enlargement of the

retroperitoneal glands, but the stomach, liver and spleen appeared to be normal. The patient made an uneventful operative recovery and lived until April 27.

*Autopsy.*—Postmortem examination performed by one of us (W. D.) was of necessity restricted to the abdominal cavity, and the report was as follows: In the upper part of the abdomen, in the region of the duodenum and pancreas, was a large, firm, grayish mass, measuring 16 cm. from the right to the left and 13 cm. from above downward, and having a maximum depth of 8 cm. Included in the removed mass were 10 cm. of the antrum of the stomach, the duodenum, the pancreas and a few centimeters of the jejunum. The total weight of the mass was 695 Gm.

Nine centimeters below the pylorus, indicated by the larger of the two arrows in figure 4, there was a complete transformation of the duodenal wall. At this point it became thickened, gray and firm. The horizontal limb of the duodenum ran straight across the midline in a rigid, tubelike fashion. When the duodenum was opened through this area, the walls were found to vary from 1 to 2.5 cm. in thickness, but they retained the same uniform color and consistency. The tumor ended more or less abruptly at about the duodenojejunal junction, and the normal jejunum beyond this point was easily invaginated with the finger into the rigid duodenum. The duodenum above the tumor was not appreciably dilated.

When the mass was cut so as to bisect the duodenum in the vertical plane, the lumen, though reduced in caliber, was fairly uniform in size. Although the tumor-infiltrated wall of the duodenum above was easily outlined, it tended to merge with the tumor, which had involved the head of the pancreas, producing distortion and thickening. Near the middle of the horizontal limb of the duodenum was a diverticulum into the tumor tissue, about 3 cm. in width and from 1.5 to 2 cm. in depth. There were also several small areas of softening. The mesenteric vessels passed through the tumor anteriorly. No visceral metastases were noted.

Microscopic examination showed a sarcomatous type of new growth with roundish cells of fairly uniform size, occasional giant cells and many mitotic figures. All of the coats of the duodenal wall were infiltrated, and in areas degeneration was in evidence.

A diagnosis of sarcoma of the duodenum (lymphosarcoma) was made.

#### COMMENT

This case is of particular interest because it marks, so far as we were able to ascertain after a careful review of the literature, the sixty-second occurrence of primary sarcoma of the duodenum. Although our case was fairly typical of similar cases recorded, we were fortunately able to perform certain clinical and laboratory tests, thus permitting a more complete record than is usually possible under similar circumstances.

No patient has been reported as cured either as a result of the surgical removal of the growth or as a result of roentgen treatment, although the latter is perhaps of value when used as a palliative measure.

#### BIBLIOGRAPHY

- Ablon, L. H.: Embryonic Fibromata (Sarcomata) of the Intestine of the Infant, Paris, 1898.  
Alexander, R. G.: Lymphomatous Tumor of the Duodenum, *Lancet* 2:954 (Dec. 29) 1877.

- Babes and Naun: Myosarcoma of the Small Intestine, *Berl. klin. Wchnschr.* **34**: 178 (Feb. 15) 1897.
- Baltzer, M.: Primary Sarcoma of the Small Intestine, *Arch. f. klin. Chir.* **44**:717, 1892.
- Barling, G.: Round Cell Sarcoma of the Small Intestine, *Ann. Surg.* **44**:242, 1907.
- Beer, E.: A Case of Primary Sarcoma of the Small Intestine, *S. Clin. North America* **5**:93 (Feb.) 1925.
- Bier, A., cited by Staemmler.
- Bjorkenheim, E.: Fibrosarcoma of the Small Intestine, *Zentralbl. f. Gynäk.* **36**:1329, 1912.
- Blumer and Bloodgood: Melanotic Sarcoma of the Small Intestine, *Bull. Johns Hopkins Hosp.* **7**:188 (Sept.-Oct.) 1896.
- Bondarew, cited by Mirotworzew and Sacharow.
- Borgherini: Primary Sarcoma of the Small Intestine, *Inaug. Dissert.*, Greifswald, 1895.
- Brandt, C., cited by Staemmler.
- Burkhardt, Ludwig: Spindle Cell Sarcoma of the Small Intestine, *Beitr. z. klin. Chir.* **34**:1, 1902.
- Carver: Generalized Melanotic Sarcoma of the Small Intestine, *Lancet* **2**:115 (July 21) 1888.
- Cavazzani, cited by Crowther.
- Cave, H. W.: Tumors of the Small Intestine, *Ann. Surg.* **96**:269 (Aug.) 1932.
- Crowther, C.: Study of Primary Carcinoma of the Small Intestine, with Report of Three Original Cases, *Clin. chir.* **21**:2107, 1913.
- David, V.: Sarcoma of the Stomach and Duodenum, *Casop. lék. česk.* **68**:1607 (Nov. 22) and 1648 (Nov. 29) 1929.
- Debrunner: Small Round Cell Sarcoma of the Small Intestine, *Inaug. Dissert.*, Zurich, 1883.
- Dulizky: Small Round Cell Sarcoma of the Small Intestine, cited by Mirotworzew and Sacharow.
- Duval, C. W.: Melanoma of Vater's Diverticulum and Lower Portion of Common Bile Duct Causing Obstruction, *J. Exper. Med.* **10**:465, 1908.
- Dynnikow, cited by Mirotworzew and Sacharow.
- Edwards: Spindle Cell Sarcoma of the Small Intestine, *Philadelphia M. Times* **3**:171, 1882-1883.
- Eiger, cited by Mirotworzew and Sacharow.
- von Esmarch, cited by Rydgyier: The Treatment of Intestinal Invaginations, *Deutsche Ztschr. f. Chir.* **42**:101, 1896.
- Fawarsky, cited by Mirotworzew and Sacharow.
- Feldman, cited by Staemmler.
- Fisher, E. M.: Round Cell Sarcoma of the Small Intestine, *M. J. Australia* **1**:337 (April 4) 1925.
- Fitz, R. H.: Round Cell Sarcoma of the Small Intestine, *Boston M. & S. J.* **92**:510 (April 29) 1875.
- Flexner, S.: Multiple Lymphosarcomata with a Report of Two Cases, *Johns Hopkins Hosp. Rep.* **3**:163, 1892-1893.
- Foxwell, A.: Fibromyxoma of the Duodenum Producing Extreme Dilatation of This and of the Stomach, *Lancet* **1**:1239 (June 22) 1889.
- Freud, J.: Roentgen Diagnosis of Typical Primary Sarcoma of the Upper Small Intestine, *Berl. klin. Wchnschr.* **53**:852 (July 31) 1916.
- Gerster, A. G., in discussion on Hitzrot: *Ann. Surg.* **63**:368 (Sept.) 1915.

- Ghon and Hintz: Malignant Leiomyoma of the Intestinal Tract, *Beitr. z. path. Anat. u. z. allg. Path.* **45**:89, 1909.
- and Roman, cited by Staemmler.
- Goebel: Round Cell Sarcoma of the Small Intestine, *Centralbl. f. Chir.* **32**:1258, 1910.
- Goldstein, H. I.: Primary Sarcoma of the Intestine: A Review of Recorded Cases, *Am. J. Surg.* **35**:240 (Oct.) and 323 (Nov.) 1921.
- Hammer, H.: Primary Multiple Tumors of Small Intestine, *Prag. med. Wchnschr.* **21**:212, 1896.
- Heinze: Dissert., Greifswald, 1897.
- Hridei, T.: Primary Sarcoma in the Small Intestine, *Zentralbl. f. Chir.* **51**:496 (March 15) 1924.
- Hulbert: Small Round Cell Sarcoma of the Small Intestine, *St. Louis M. & S. J.* **48**:250 (Feb. 28) 1885.
- Illoway, H.: Early Diagnosis of Neoplasms in the Intestinal Tract and Their Localization, *Arch. f. Verdauungskr.* **38**:87 (April) 1926.
- Kasemeyer, E.: Tumor Invagination of the Intestines, *Deutsche Ztschr. f. Chir.* **118**:205, 1912.
- Kathe, H., cited by Staemmler.
- Kohn, H.: Melanotic Sarcoma of the Small Intestine, *Deutsche med. Wchnschr.* **33**:1194 (July 18) 1907.
- Kompe, cited by Crowther.
- Kotschanow: Dissert., 1906.
- Lange, K.: Fibrosarcoma of the Small Intestine, *Hygica* **2**:372, 1902.
- LaRoque, G. P., and Shifflett, E. L.: Tumors of the Duodenum, *Ann. Surg.* **98**:178 (Aug.) 1933.
- Latzel, R., cited by Staemmler.
- Libman, E.: Sarcoma of the Small Intestine, *Am. J. M. Sc.* **120**:309, 1900.
- Lymphosarcoma, *Am. J. M. Sc.* **129**:813, 1905.
- MacKenzie, H. M., cited by Staemmler.
- MacKenzie, J. C.: Melanotic Sarcomatosis, *Brit. M. J.* **1**:907 (April 25) 1891.
- Madelung, cited by Baltzer.
- Mandelbaum and Libman, cited by Staemmler.
- Mattison: General Melanotic Sarcoma of the Small Intestine, *Deutsche med. Wchnschr.* **15**:743 (Sept. 15) 1889.
- Mayr, G., cited by Staemmler.
- Miller, C. J.: Sarcoma of the Duodenum, *New Orleans M. & S. J.* **78**:27 (July) 1925.
- Mirotworzew, S. R., and Sacharow, N. W.: Zur Pathologie und Klinik der Darmsarkome, *Arch. f. klin. Chir.* **130**:256, 1924.
- Moore, N. F.: Sarcoma Involving the Duodenum, *Lancet* **1**:13 (Jan. 6) 1883.
- Mosher, B. B.: Some Clinical Variations of Sarcoma, with Report of a Rapidly Fatal Case, *Brooklyn M. J.* **18**:226 (June) 1904.
- Mostowska: Globe-Cellular Sarcoma of the Duodenum, *Polska gaz. lek.* **6**:250 (March 27) 1927.
- Nemilow, cited by Mirotworzew and Sacharow.
- Nicholaysen, C.: Myosarcoma of the Small Intestine, *Norsk mag. f. lægevidensk.* **15**:12, 1886.
- Perez, G.: Round Cell Sarcoma, *Arch. ital. di chir.* **3**:181 (March 5) 1920.
- Perry, E. C., and Shaw, L. C.: Diseases of the Duodenum, *Guy's Hosp. Rep.* **50**:171, 1893.



- Petrow, cited by Mirotworzew and Sacharow.
- Pfundt, W.: Spindle Cell Sarcoma of the Duodenum, *Arch. f. klin. Chir.* **163**:488, 1931.
- Rademacher: Primary Sarcoma of the Small Intestine, Inaug. Dissert., Jena, 1908.
- Raiford, T. S.: Tumors of the Small Intestine, *Arch. Surg.* **25**:122 (July) and 321 (Aug.) 1932.
- Renner: *Zentralbl. f. Chir.* **38**:913, 1912.
- Robb, D.: Sarcoma of the Small Intestine, *Brit. M. J.* **2**:1007 (Nov. 30) 1929.
- Rodsiewsky, cited by Mirotworzew and Sacharow.
- Rolleston: Sarcoma of the Duodenum, *Brit. M. J.* **1**:70 (Jan. 9) 1892.
- von Salis: Sarcoma of the Duodenum, Especially Myosarcoma, *Deutsche Ztschr. f. Chir.* **160**:180 (Dec.) 1920.
- Schapiro, cited by Mirotworzew and Sacharow.
- Schmidt, E.: Lymphomatosis of the Small Intestine, *Frankfurt. Ztschr. f. Path.* **16**:131, 1915.
- Shifflett, E. I.: Tumors of the Duodenum and Hypertrophied Gastric Mucosa Prolapsing Through the Pyloric Canal into the Duodenum, *Radiol.* **9**:79 (Aug.) 1932.
- Smith, cited by Kasemeyer.
- Smoler, cited by Kasemeyer.
- Soli, D.: Primary Sarcoma of the Duodenum, *Clin. chir.* **33**:887 (Aug.) 1930.
- Staemmler, Martin: Neoplasms of the Intestine, in von Bruns, P.: *Neue Deutsche Chirurgie*, Stuttgart, Ferdinand Enke, 1925, vol. 36.
- Storch, B., cited by Staemmler.
- Strauss, A. A.; Block; Fried, and Hamburger: Sarcoma of the Duodenum and Stomach, *S. Clin. North America* **5**:977 (Aug.) 1925.
- Ullman, A., and Abeshouse, B. S.: Lymphosarcoma of Small and Large Intestines, *Ann. Surg.* **95**:878 (June) 1932.
- Valdes: Thèse de Paris, 1897-1898.
- Verebely, cited by Staemmler.
- Vonwyl, cited by Staemmler.
- Waldenstrom and Akerberg, cited by Baltzer.
- Weeden, W. M.: Lymphosarcoma of the Gastro-Intestinal Tract, with Report of Thirteen Cases, *Ann. Surg.* **110**:247, 1929.
- Wesener, F.: Case Reports of Tumors, *Virchows Arch. f. path. Anat.* **93**:377, 1883.
- Wolfram: A Case of Duodenal Sarcoma, *St. Petersburg. med. Wehnschr.* **9**:2, 1902; abstr., *Zentralbl. f. Chir.* **29**:506, 1902.
- Wolkowitsch, cited by Mirotworzew and Sacharow.
- Zuralski, V.: Contribution to the Case Reports of Tumors of the Small Intestine. *Dissert., Königsberg*, 1889.

# EXPERIMENTAL PULMONARY EMBOLISM ASSOCIATED WITH VENOCLYSIS

MERVIN J. RUMOLD, M.D.

KANSAS CITY, KAN.

Since the World War there has been an increased popularity of the continuous intravenous injection of drugs and fluids, and, coincidentally, there has been a rise in the incidence of pulmonary embolism. During the last three or four years the medical journals have contained much concerning the value of continuous venoclysis, but little has been written of its dangers. Recently I have noted an association of pulmonary complications with continuous venoclysis in some of my patients. It is my purpose to present experimental evidence showing the direct relationship between pulmonary embolism and venoclysis. No experimental work on this subject has been noted in the literature.

Michaelis,<sup>1</sup> in 1910, was the first to suggest that death resulting from the administration of arsphenamine was due to precipitates in the blood after the injection of the drug. Shivers,<sup>2</sup> in 1933, collected twenty-two cases of pulmonary embolism following the injection of sclerosing substances intravenously for the obliteration of varicose veins; seventeen of the twenty-one patients died. Bsteh and Teichmann<sup>3</sup> reported three cases of lung emboli associated with the treatment of varicose veins of the leg by injection. They stated that thrombosis and embolism are not extremely rare in the treatment of varicose veins, and requested that more reports be made in order that a true picture of the complication might be gained and statistics compiled.

Orator and Schleusing<sup>4</sup> recorded a case which at autopsy revealed pulmonary emboli following the continuous injection of dextrose solution through the median basilic vein in the left cubital fossa. The median basilic vein contained an organizing thrombus, and the authors expressed the belief that this served as an origin of the emboli. They

---

From the School of Medicine, University of Kansas.

This study was made in partial fulfilment of the requirement for the degree of Master of Science in Surgery, University of Kansas.

1. Michaelis, L.: Die Ehrlich-Hata Behandlung in der inneren Medizin, *Deutsche med. Wchnschr.* **36**:2278, 1910.

2. Shivers, G. C.: Pulmonary Embolism from Arsenicals Injected Intravenously: Method Suggested for Prevention, *Arch. Dermat. & Syph.* **27**:901 (June) 1933.

3. Bsteh, W., and Teichmann, M.: Pulmonary Emboli Developing After Injection Treatment of Varicose Veins, *Zentralbl. f. Chir.* **60**:376 (Feb. 18) 1933.

4. Orator, V., and Schleusing, H.: Thrombose und Hirnemboli infolge intravenöser Dauertropfinfusion, *Zentralbl. f. Chir.* **57**:2530 (Oct. 11) 1930.

believed that thrombi form at the site of entrance of the cannula and are due to the irritation of the wall of the vessel produced by the cannula. They also noted that there are many reports of others who have found no thrombi or emboli at autopsy in cases in which continuous infusions were used, but they expressed the opinion that evidences would be found if a more thorough search were made. In spite of the danger noted, they advised the use of infusions in cases in which quick relief is called for, but recommended as a precautionary measure that the arm be immobilized by fixation to a splint. They also stated that the general use of continuous venoclysis in all cases should be discouraged and that the procedure should be used only when other methods fail.

Friedrich and Buchaly<sup>5</sup> have described two cases of pulmonary embolism following continuous venoclysis.

One case they reported was that of a man, 58 years of age, who had been operated on for carcinoma of the stomach. The intravenous administration of dextrose was started, and the solution was allowed to flow into the median basilic vein for two days, when suddenly the patient became dyspneic. He made a temporary recovery but the following day had two similar attacks and died. At autopsy, multiple pulmonary thrombi were found, and the histologic examination of the vein which was used for the venoclysis revealed a thickened wall with numerous leukocytes throughout. Attached to the intima of the vein was an organizing thrombus. No bacteria were found. The authors stated that the thrombus was due to mechanical injuries to the wall of the vessel.

Friedrich and Buchaly suggested: that infusions be given over shorter periods of time; that the site of injection be changed frequently; that the solutions, as nearly as possible, be the same in composition and specific gravity as the blood, and, last, that this type of therapy be used only when strongly indicated. Strauss<sup>6</sup> wrote that complications of the vascular system following the use of continuous infusions have increased with the wider use of this method. "Venous thrombosis and thrombophlebitis have increased in spite of the assumption by many that continuous intravenous therapy is harmless." He reported the case of a patient who underwent an operation for disease of the gallbladder and died suddenly after having received continuous venoclysis for five days postoperatively. A thrombus, 6 cm. long and 1.2 cm. thick, was found in the pulmonary artery. The veins of the lower extremities were free from thrombi. A thrombus was found extending up to the axillary vein from the site of the injection. Many leukocytes were noted deep in the wall of the vessel. Strauss expressed the belief that the pulmonary embolism was undoubtedly due to the continuous infusion and warned against its use.

5. Friedrich, H., and Buchaly, J. F.: Ist die intravenöse Dauertropfinfusion mit Gefahren verbunden? *Zentralbl. f. Chir.* 59:131 (Jan. 16) 1932.

6. Strauss, Ludwig: Thrombose und Lungenembolie nach intravenöser Dauertropfinfusion, *Zentralbl. f. Chir.* 59:909 (April 2) 1932.

Pulmonary embolism in this study has been considered the metastasis of suspended clotted elements of the blood by way of the right side of the heart to the lesser circulation, with impaction in the pulmonary artery. Of the various embolic possibilities, I am limiting my report to thrombi arising from the venous side of the circulation associated with continuous venoclysis.

In the experimental work, six series of dogs were used for the study of pulmonary embolism associated with venoclysis.

TABLE 1 (Series 1).—*Observations on Dogs Which Were Restrained and Given Morphine and Received 10 per Cent Solution of Dextrose in Physiologic Solution of Sodium Chloride by Continuous Venoclysis Through a Cannula Inserted in the Saphenous Vein*

No. of Dog	Duration of Life, Days	Observations	
		Vein at Site of the Cannula	Lungs
1	10	Organizing thrombus	Pulmonary infarcts and thrombi
2	13	Organizing thrombus	Pulmonary infarcts and thrombi

TABLE 2 (Series 2).—*Observations on Dogs Partially Restrained and Given 10 per Cent Solution of Dextrose in Physiologic Solution of Sodium Chloride by Continuous Venoclysis Through a Cannula Inserted in One Jugular Vein*

No. of Dog	Duration of Life, Days	Observations	
		Vein at Site of the Cannula	Lungs
1	13	Organizing thrombus	Pulmonary infarcts; no thrombi
2	18	Organizing thrombus	Pulmonary infarcts and thrombi
3	6	Organizing thrombus	Pulmonary infarcts and thrombi
4	16	Organizing thrombus	Pulmonary infarcts and thrombi
5	12	Organizing thrombus	Pulmonary infarcts; no thrombi
6	10	Organizing thrombus	Pulmonary infarcts and thrombi

#### EXPERIMENTAL PROCEDURE

Series 1 (table 1) consisted of two dogs, which were restrained on a table. One hindleg of each dog was shaved and surgically prepared. The saphenous vein was exposed, and a ureteral catheter was inserted and securely anchored within the lumen. A 10 per cent solution of dextrose in physiologic solution of sodium chloride was allowed to drip slowly and continuously through the catheter at the rate of from 10 to 12 drops a minute. The apparatus for venoclysis resembled in every respect the type used in giving patients continuous infusions. Considerable difficulty was encountered in keeping the dogs quiet. Morphine was given in  $\frac{1}{4}$  grain (16.2 mg.) doses every two hours. The dogs were watched day and night by an attendant who checked the flow of the solutions every hour.

For series 2 (table 2), which consisted of six dogs, individual wire cages with floors of wire netting were employed. Each animal was partially restrained by a short leash which was attached to a collar around his neck and to one corner

of the cage (fig. 1). The dogs were allowed a small range of motion and could even stand erect without interfering with the experiment. Morphine was not administered. For the cannula I used a no. 12F soft rubber catheter, with the tip cut obliquely. A rubber guard, measuring 1 cm. in length, was cut from a no. 14F soft rubber catheter. The no. 12 catheter was threaded through the lumen

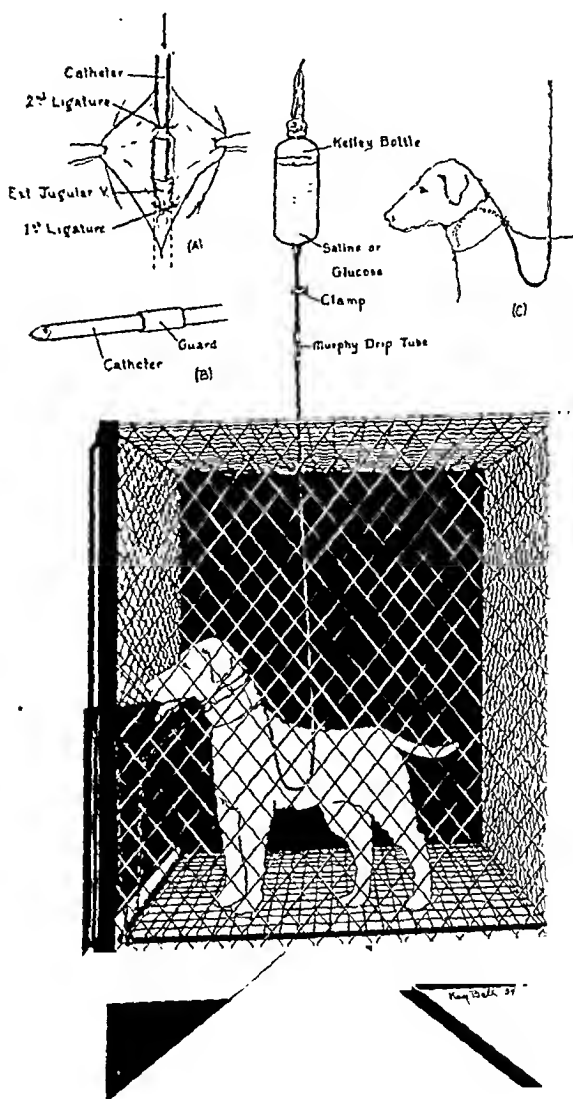


Fig. 1.—A sketch showing the method of administering continuous venoclysis to dogs. The inserts show the method of insertion of the cannula (no. 12F rubber catheter) into the jugular vein.

of the guard so that the guard was located 2 cm. from the tip of the cannula (insert in fig. 1). The neck of each dog was surgically prepared and with the animal under light ether anesthesia a surgical incision exposed an external jugular vein. The no. 12 soft catheter with the attached guard was inserted into the lumen of the vein for a distance of 2 cm. so that the guard came in contact with

the opening in the vein. The cannula was anchored securely by a ligature around the vein and a cannula on each side of the guard (insert in fig. 1). The skin incision was closed with sterile catgut and a wide piece of sterile adhesive tape was applied around the neck over the incision, almost completely incorporating the tube of the cannula (insert in fig. 1). Little difficulty was encountered in keeping the dogs quiet and the solutions flowing freely. The flow of the solution was checked approximately every hour by an attendant, who stayed with the dogs day and night. No food or water was given by mouth. A 10 per cent solution of dextrose in physiologic solution of sodium chloride was permitted to drip slowly and continuously through the cannula at the rate of from 10 to 15 drops a minute.

Series 3 (table 3), which consisted of three dogs, received physiologic solution of sodium chloride by venoclysis. The method used was identical with that used

TABLE 3 (Series 3).—*Observations on Dogs Partially Restrained and Given 10 per Cent Solution of Dextrose by Continuous Venoclysis Through a Cannula Inserted in One Jugular Vein*

No. of Dog	Duration of Life, Days	Observations	
		Vein at Site of the Cannula	Lungs
1	10	Organizing thrombus	Pulmonary infarcts and thrombi
2	12½	Organizing thrombus	Pulmonary infarcts and thrombi
3	8	Organizing thrombus	Pulmonary infarcts and thrombi

TABLE 4 (Series 4).—*Observations on Dogs Partially Restrained and Given Physiologic Solution of Sodium Chloride by Continuous Venoclysis Through a Cannula Inserted in One Jugular Vein*

No. of Dog	Duration of Life, Days	Observations	
		Vein at Site of the Cannula	Lungs
1	14	Organizing thrombus	Pulmonary infarcts and thrombi
2	16	Organizing thrombus	Pulmonary infarcts; no thrombi
3	10	Organizing thrombus	Pulmonary infarcts and thrombi

for the dogs of series 2. The object of the experiment was to determine if an isotonic solution of sodium chloride showed any difference in the production of thrombi and emboli, as compared with a solution of dextrose or with a combination of dextrose and physiologic solution of sodium chloride.

Series 4 (table 4), which consisted of three dogs, received a 10 per cent solution of dextrose in distilled water by venoclysis. The method employed was identical with that used for series 2. The results of this experiment were to be compared with those obtained on series 3.

Series 5 (table 5) consisted of three dogs. The experiment was planned to determine what effect the mere presence of a cannula lodged in the vein had in the production of thrombosis and pulmonary emboli and whether one type of cannula was more instrumental in producing thrombosis than other commonly used types. A no. 18 sharp steel needle was inserted into the lumen of the external jugular vein of one dog, a gold cannula into that of another and a rubber catheter into that of the third. The skin and subcutaneous tissue were closed with sterile catgut, and sterile dressings were applied over the incisions.

Series 6 (table 6) consisted of two dogs. The experiment was planned to determine the effect produced on the lungs of normal dogs when blood clots were released in the venous side of the circulation. With the animal under light ether anesthesia one of the external jugular veins was exposed. A glass cannula, measuring 6 cm. in length and 0.5 cm. in diameter, was inserted into the jugular vein and was securely anchored. A syringe containing physiologic solution of sodium chloride was attached to the open end of the cannula. Blood was allowed to fill and clot in the cannula for one-half hour. After the blood had clotted it was forced back into the circulation by pressure from the attached syringe. The incision was closed with aseptic technic. The dogs were killed at the end of six and eight days.

# PROTOCOLS

*Series 1.*—Dog 1.—A white female dog, which weighed 9.1 Kg. before the experiment, died in ten days.

TABLE 5 (*Series 5*).—*Observations on Dogs in Each of Which One of the Commonly Used Cannulas Was Inserted into the Lumen of the External Jugular Vein*

No. of Dog	Cannula	Duration of Life, Days	Observations	
			Vein at Site of Cannula	Lungs
1	Steel	8	Organizing thrombus	Pulmonary infarcts and thrombi
2	Gold	10	Organizing thrombus	Pulmonary infarcts and thrombi
3	Rubber	10	Organizing thrombus	Pulmonary infarcts and thrombi

TABLE 6 (*Series 6*).—*Observations on Dogs Having Apparently Normal Lungs in Which Well Formed Clots Were Released into One Jugular Vein*

No. of Dog	No. of Days Before Killed	Observations on the Lungs
1	6	Pulmonary thrombi; no infarcts
2	8	Pulmonary thrombi; no infarcts

At autopsy the weight of the dog was 8.2 Kg. Emaciation was very marked. An examination of the saphenous vein at the site of the injection of the solution revealed a small quantity of free pus. The tissue surrounding the vein was edematous. The wall of the vein was thickened, and the lumen was partially occluded by an attached thrombus which extended distal from the tip of the cannula. The right lung weighed 86 Gm., and the left lung, 72 Gm. The lungs were moderately crepitant except for a few firm, triangular, hemorrhagic infarcts which had their bases directed peripherally. The lower lobes were edematous and firm.

Microscopic examination of the saphenous vein revealed an attached organizing thrombus. The wall of the vein was thickened, and throughout the wall were numerous polymorphonuclear leukocytes. Foci of leukocytes were seen throughout the areolar tissue surrounding this vein. Sections of the lungs showed typical hemorrhagic infarcts. The framework of the lungs was edematous and thickened. No pneumonia was noted.

The diagnosis was: acute phlebitis and thrombosis of the saphenous vein, pulmonary infarcts and pulmonary edema.

Dog 2.—A spotted male dog, which weighed 10.4 Kg. before the experiment, lived for thirteen days.

At autopsy the dog weighed 9.1 Kg. Emaciation was pronounced. An examination of the saphenous vein at the site of the insertion of the cannula showed some free pus in the wound. The perivascular tissue surrounding the vein was edematous, and the wall of the vein was thickened. Attached to the wall of the vein and partially occluding the lumen was a thrombus. The right lung weighed 110 Gm., and the left lung, 90 Gm. Both lungs appeared to be edematous. Numerous dark red areas were noted over the pleural surfaces. Section through the red areas showed typical triangular hemorrhagic infarcts.

Microscopic section of the saphenous vein revealed an attached organizing thrombus located distal to the tip of the cannula. The wall of the vein was definitely thickened and infiltrated with many polymorphonuclear leukocytes. The lungs revealed multiple hemorrhagic infarcts and thrombi in some of the pulmonary vessels. Many of the bronchi and some of the alveoli contained polymorphonuclear leukocytes. In some places the bronchial mucosa had been broken down, and the fragmented epithelium was seen in the lumen of the bronchi.

The diagnosis was: acute phlebitis and thrombosis of the saphenous vein, hemorrhagic pulmonary infarcts and bronchopneumonia.

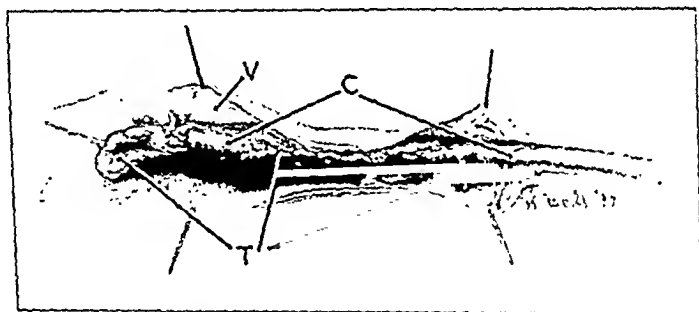


Fig. 2.—A drawing showing extensive thrombosis of the external jugular vein of a dog which had received a solution of dextrose in physiologic solution of sodium chloride by continuous venoclysis for eighteen days. In this and the succeeding illustrations *T* indicates the thrombus, *V*, the wall of the vessel, and *C*, the catheter.

*Series 2.—Dog 1.*—A brown male dog, which weighed 10.4 Kg. before the experiment, died after eighteen days.

At autopsy the dog weighed 9 Kg. An examination of the site of the injection of the solution revealed definite evidence of infection. Free pus was seen around the external jugular vein in the region of the cannula. The perivascular tissue also showed considerable induration. The lumen was partially occluded by an attached blood clot which extended distal from the tip of the cannula (fig. 2). The right lung weighed 100 Gm., and the left lung, 93 Gm. Multiple infarcts were seen in both lungs. The lungs were moderately crepitant except their lower lobes, which appeared to be very edematous. A cross-section through the lungs showed multiple irregular small hemorrhagic infarcts.

Microscopic section of the external jugular vein just distal to the tip of the cannula showed an organizing thrombus attached to the intima (fig. 3). The wall was thickened, and the areolar tissue surrounding the vein was edematous. Numerous polymorphonuclear leukocytes were seen throughout the wall of the vein. Microscopic section of the lung showed an unusual picture. There were multiple



pulmonary infarcts associated with pulmonary thrombi. In addition, infiltrated throughout the infarcted lung tissue were numerous yellow-staining segmented filaments of fungus. Some of the bronchi contained pus cells, while others were free from infection. A few of the alveoli surrounding the infected bronchi contained pus cells.

The diagnosis was: acute phlebitis and an organizing thrombus of the external jugular vein, multiple pulmonary infarcts and thrombi, mycotic infection of the lungs (fungus) and beginning bronchopneumonia.

Dog 2.—A black female dog, which weighed 10 Kg. before the experiment, lived for six days.

At autopsy the dog weighed 9.6 Kg. An examination of the tissue at the site of the injection of the solution showed no free pus. The perivascular tissue around the external jugular vein was thickened and was partially occluding the lumen.

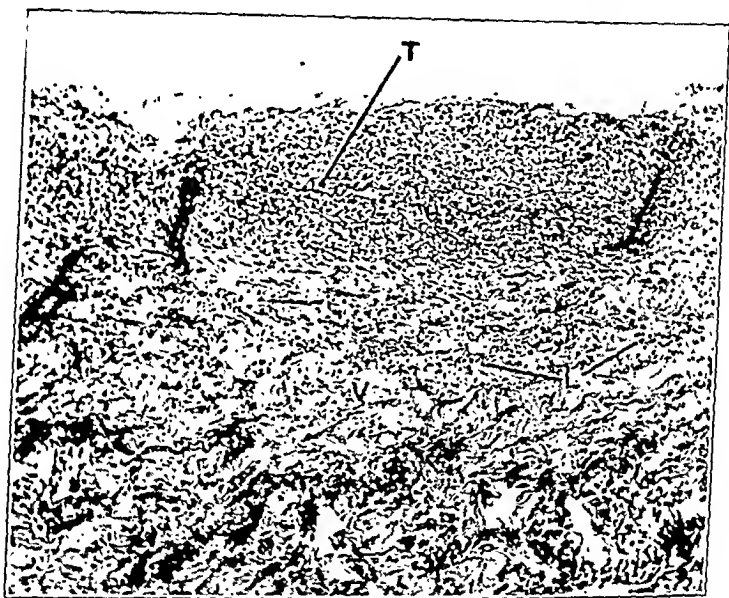


Fig. 3.—A photomicrograph of the external jugular vein of a dog taken just distal to the tip of the cannula through which a 10 per cent solution of dextrose in physiologic solution of sodium chloride had been introduced for eighteen days. Note the attached thrombus and the acute inflammatory reaction throughout the wall of the vein. *L* indicates polymorphonuclear leukocytes.

Extending distal to the tip of the cannula was a thrombus. The right lung weighed 88 Gm., and the left lung, 82 Gm. The lungs were nodular, and the pleural surface was red and mottled. The lungs were extremely moist. A section through the nodules showed typical irregular pulmonary infarcts. A section through one infarct showed a thrombus in one of the pulmonary vessels.

Microscopic section through the wall of the external jugular vein just distal to the tip of the cannula revealed an organizing thrombus which partially occluded the lumen of the vein. There was considerable thickening of the wall of the vein and the areolar tissue surrounding the vein. Many polymorphonuclear leukocytes were seen throughout the wall. The lungs showed multiple hemorrhagic infarcts, and some of the vessels contained thrombi (fig. 4). Some of the bronchi showed a breaking down of the mucosa, and in a few of the bronchi polymorpho-

nuclear leukocytes were found. Pus cells filled some of the alveolar spaces adjacent to the infected bronchi.

The diagnosis was: acute phlebitis and an organizing thrombus of the external jugular vein, multiple pulmonary infarcts and thrombi and beginning bronchopneumonia.

Dog 3.—A white female dog, which weighed 7.7 Kg. before the experiment, died at the end of sixteen days.

At autopsy the dog weighed 7 Kg. An examination of the tissue at the site of the injection revealed no gross evidence of infection. The perivascular tissues around the external jugular vein which had received the continuous venoclysis showed edema and induration. The wall of the vein was thickened, and attached to the wall and extending distal to the tip of the cannula was a thrombus. The right lung weighed 75 Gm. and the left lung, 62 Gm. Both lungs were crepitant



Fig. 4.—A photomicrograph of a portion of the lung of a dog which had received a 10 per cent solution of dextrose in physiologic solution of sodium chloride by venoclysis for six days. Note the thrombus lodged within the pulmonary artery and the surrounding pulmonary infarct.

except for firm nodular areas. A section through the nodules showed numerous hemorrhagic infarcts, some of which were triangular and had their bases directed peripherally.

Microscopic section through the wall of the external jugular vein just distal to the tip of the cannula revealed an attached organizing thrombus, which partially occluded the lumen of the vessel. There was considerable thickening of the wall of the vein and the areolar tissue surrounding the vein. Many polymorphonuclear leukocytes were seen throughout the wall. Microscopic sections of the lungs showed multiple pulmonary infarcts, and some of the vessels were occluded with thrombi. A few of the bronchi and adjacent alveoli were filled with pus cells. The framework of the lungs was edematous, the vessels were congested, and many of them contained pus cells.

The diagnosis was: acute phlebitis and thrombosis of the external jugular vein with partial occlusion, multiple pulmonary infarcts and thrombi and beginning bronchopneumonia.

Dog 4.—This dog, which weighed 10.4 Kg. before the experiment, died after twelve days.

At autopsy the weight of the dog was 9.2 Kg. Examination of the operative site in the region of the injection revealed no gross evidence of infection. The tissue surrounding the vein was edematous and indurated. The wall of the vein was thickened. Attached to the intima and extending distal to the tip of the cannula was a thrombus. The right lung weighed 105 Gm., and the left lung, 90 Gm. The lungs were moderately crepitant except for a few nodular areas which on cross-section revealed hemorrhagic infarcts, a few of which were triangular.

Microscopic section of the external jugular vein just distal to the tip of the cannula revealed a thickening of the wall, and attached to the intima was an organizing thrombus. Infiltrated throughout the wall were numerous polymorphonuclear leukocytes. Microscopic examination of the lungs revealed hemorrhagic infarcts and thrombi. Here and there were patchy areas in which pus cells filled the bronchi and adjacent alveoli. The framework of the lungs was very edematous.

The diagnosis was: acute phlebitis and thrombosis of the external jugular vein with partial occlusion, multiple pulmonary infarcts and thrombi and bronchopneumonia.

Dog 5.—A brown male dog, which weighed 10.9 Kg. before the experiment, died at the end of ten days.

At autopsy the weight was 9.6 Kg. An examination at the site of the injection revealed no evidence of infection. The perivascular tissue surrounding the external jugular vein was edematous and indurated. The wall of the vein was thickened, and attached to the wall and extending distal to the tip of the cannula was a thrombus which partially occluded the lumen. The right lung weighed 93 Gm. and the left lung, 85 Gm. Both lungs were moderately crepitant except for some nodular areas which on cross-section showed multiple hemorrhagic infarcts.

Microscopic sections of the external jugular vein just distal to the point at which the cannula was inserted revealed a thickening of the wall, and attached to the wall was an organizing thrombus which partially occluded the lumen of the vein (fig. 5). Throughout the wall of the vein were numerous polymorphonuclear leukocytes. Microscopic sections of the lungs showed numerous hemorrhagic infarcts, but no thrombi were seen in the pulmonary vessels. The framework of the lung was edematous, and scattered throughout the lung tissue were numerous irregular patches in which the bronchi and adjacent alveoli were filled with pus cells.

The diagnosis was: acute phlebitis and thrombosis of the external jugular vein with partial occlusion, multiple pulmonary infarcts and beginning pneumonia.

Dog 6.—A female collie, which weighed 11.4 Kg. before the experiment, died in twelve days.

At autopsy the weight was 10.6 Kg. An examination of the tissue surrounding the vein in which the cannula had been inserted revealed no evidence of infection. The perivascular tissue was thickened and indurated. The wall of the vein was thickened, and attached to the wall and extending distal to the tip of the cannula was a fragile clot which partially occluded the lumen. The right lung weighed 96 Gm., and the left lung, 82 Gm. Both lungs were nodular and edematous. Sections of the nodular areas showed hemorrhagic infarcts.

Microscopic examination of the external jugular vein just distal to the tip of the cannula revealed a thickened wall in which there were numerous polymorphonuclear leukocytes. Attached to the intima and partially occluding the lumen was an organizing thrombus. Microscopic examination of the lungs revealed multiple pulmonary thrombi with suggestive pulmonary infarcts. No evidence of pneumonia was noted.

The diagnosis was: acute phlebitis and thrombosis of the external jugular vein and multiple pulmonary thrombi.

*Series 3.—Dog 1.*—A spotted black and white female dog, which weighed 10.3 Kg. before the experiment, died at the end of ten days.

At autopsy the weight was 9.1 Kg. An examination of the incision and tissues in the vicinity in which the venoclysis had been given revealed no evidence of infection. The perivascular tissue surrounding the external jugular vein was



Fig. 5.—A photomicrograph of the external jugular vein of a dog taken just distal to the tip of the cannula through which a 10 per cent solution of dextrose in physiologic solution of sodium chloride had been introduced for ten days. Note the attached thrombus (T) and the inflammatory reaction in the wall of the vein.

edematous and indurated. The wall of the vein was thickened, and attached to the wall and extending distal from the tip of the cannula was a fragile thrombus. The right lung weighed 86 Gm., and the left lung, 72 Gm. Both lungs revealed moderate crepitation, with the exception of a few firm red nodules. A section through the nodular lung tissue showed well defined infarcts. Some of the pulmonary infarcts were triangular and had their bases directed peripherally. The bronchi were filled with a purulent material.

Microscopic examination of the external jugular vein distal to the point of the cannula revealed an organizing thrombus which partially occluded the lumen of the vessel. The wall of the vessel was thickened, and infiltrated throughout were numerous polymorphonuclear leukocytes. Microscopic examination of the lungs revealed multiple pulmonary infarcts, with one suggestive pulmonary thrombus.

The framework of the lungs was edematous and swollen. In a few places polymorphonuclear leukocytes were seen filling the bronchi and adjacent alveolar spaces.

The diagnosis was: acute phlebitis and thrombosis of the external jugular vein, multiple pulmonary infarcts and beginning pneumonia.

Dog 2.—A male collie, which weighed 11.6 Kg. before the experiment, lived for twelve and one-half days.

At autopsy the weight was 10.6 Kg. Examination of the external jugular vein at the site of the injection showed no evidence of infection. The tissue around the vein was thickened and indurated. The vein was thickened, and within the lumen and extending distally to the tip of the cannula was a fragile thrombus which partially occluded the lumen. The right lung weighed 92 Gm., and the left lung, 84 Gm. Both lungs were moderately crepitant except for a few nodular areas which on cross-section revealed irregular hemorrhagic infarcts.

Microscopic examination of the external jugular vein just distal to the tip of the cannula revealed a thickening of the wall, which was infiltrated by polymorphonuclear leukocytes. Attached to the intima and partially occluding the lumen was an organizing thrombus. Polymorphonuclear leukocytes were also seen in the areolar tissue surrounding the vein. Microscopic examination of the lungs revealed multiple pulmonary infarcts associated with pulmonary thrombi. Some of the thrombi appeared to be organizing, and in one canalization was seen. A few of the bronchi and surrounding alveoli contained pus cells.

The diagnosis was: acute phlebitis and thrombosis of the external jugular vein, multiple pulmonary infarcts and pulmonary thrombi and early bronchopneumonia.

Dog 3.—A brown male dog, which weighed 8.3 Kg. before the experiment, died at the end of eight days.

At autopsy examination of the external jugular vein at the site of the injection revealed no evidence of pus. The perivascular tissue in this region was swollen and indurated. The wall of the vein was thickened, and attached to the wall and partially occluding the lumen and extending distal from the tip of the cannula was a fragile thrombus. The right lung weighed 78 Gm., and the left lung, 62 Gm. Both lungs were moderately crepitant except for two small firm nodular areas. A section through these nodular areas revealed typical hemorrhagic infarcts.

Microscopic examination of the external jugular vein distal to the point of the catheter revealed a thickening of the wall, and infiltrated throughout were numerous polymorphonuclear leukocytes. Attached to the intima and partially occluding the lumen was an organizing thrombus. Microscopic examination of the lungs revealed typical hemorrhagic pulmonary infarcts associated with pulmonary thrombi. Some of the bronchi and surrounding alveoli contained numerous polymorphonuclear leukocytes. The vessels were engorged, and many of them contained pus cells.

The diagnosis was: acute phlebitis and thrombosis of the external jugular vein, multiple pulmonary infarcts and thrombi and bronchopneumonia.

Series 4.—Dog 1.—A male dog, which weighed 7 Kg. before the experiment, died after fourteen days.

At autopsy the weight was 6.2 Kg. Examination of the external jugular vein at the site of the injection revealed no free pus. The perivascular tissue surrounding the vein was edematous and indurated. The wall of the vessel was thickened. Within the lumen of the vessel and extending distal from the tip of the catheter and partially occluding the lumen of the vein was a fragile thrombus. The right lung weighed 75 Gm., and the left lung, 70 Gm. Both lungs were moderately crepitant throughout except for a few red nodular areas. A cross-section

revealed several red irregular hemorrhagic infarcts. A few of the infarcts were triangular and had their bases directed peripherally.

Microscopic examination of the vein at the site of the injection revealed an organizing thrombus which partially occluded the lumen of the vessel. The vessel was thickened, and throughout its wall were numerous polymorphonuclear leukocytes. Microscopic examination of the lungs revealed large red hemorrhagic infarcts. No definite pulmonary thrombi were noted.

The diagnosis was: acute phlebitis and thrombosis of the external jugular vein, and pulmonary infarcts.

Dog 2.—A white dog, which weighed 10 Kg. before the experiment, died after sixteen days.

At autopsy the weight was 9.4 Kg. Examination of the tissues at the site of the injection revealed no evidence of pus. The perivascular tissue around the

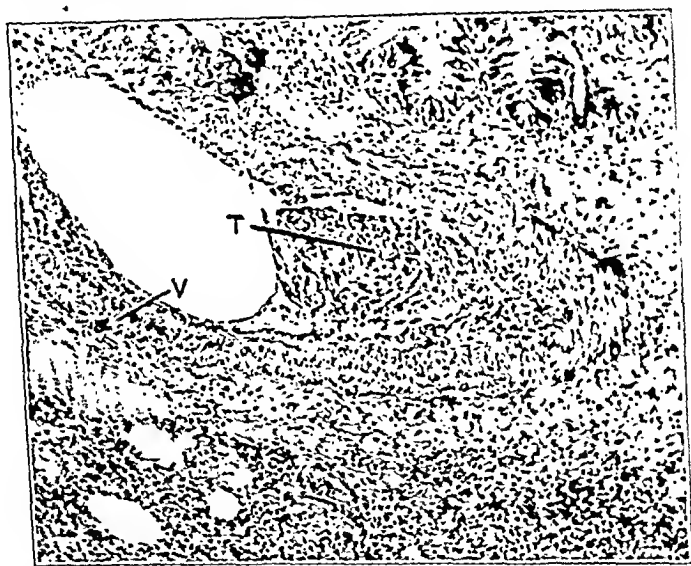


Fig. 6.—A photomicrograph of a section of the lung of a dog which received physiologic solution of sodium chloride by venoclysis for ten days. The pulmonary thrombus shows organization and canalization.

vessel was edematous and indurated. The wall of the vessel was thickened, and within the lumen was a thrombus partially occluding the lumen and extending distally from the tip of the cannula. The right lung weighed 92 Gm., and the left lung, 80 Gm. Both lungs were moderately crepitant except for a few firm nodules. A section through one of the nodular areas revealed a red hemorrhagic infarct. No gross pulmonary thrombi were noted.

Microscopic examination of the wall of the external jugular vein just distal to the tip of the cannula revealed a thickened wall; polymorphonuclear leukocytes were seen throughout the wall, and there was a thrombus within the lumen, partially occluding it. Microscopic examination of the lungs revealed no definite pulmonary infarcts. The framework of the lungs was very edematous. Some of the bronchi and surrounding alveoli contained polymorphonuclear leukocytes. One vessel showed a pulmonary thrombus.

The diagnosis was: acute phlebitis and thrombosis of the external jugular vein, pulmonary thrombus and bronchopneumonia.

Dog 3.—A female dog, which weighed 10.8 Kg. before the experiment, lived for ten days.

At autopsy the weight was 9.5 Kg. Examination of the tissues in the region of the external jugular vein at the site of the injection revealed no free pus. The perivascular tissue around the external jugular vein showed some thickening and some induration. The wall of the vessel was thickened, and within the lumen, extending distally from the cannula and partially occluding the lumen, was a thrombus. The right lung weighed 92 Gm., and the left lung, 82 Gm. Both lungs were moderately crepitant. There were numerous small irregular hemorrhagic infarcts.

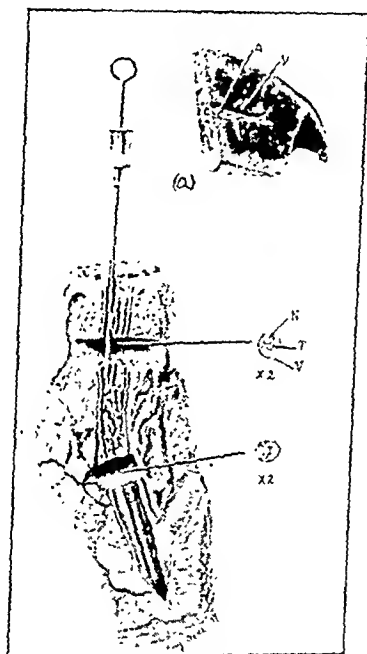


Fig. 7.—A drawing showing the results of the presence of a steel needle lodged in the lumen of the external jugular vein of a dog. Note the thrombus attached to the wall and the insert showing a pulmonary infarct associated with a pulmonary thrombus.

Microscopic examination of the vein distal to the site of the injection revealed an organizing thrombus which was attached to the wall of the vessel and partially occluded the lumen. The wall of the vessel was thickened, and infiltrated throughout were some polymorphonuclear leukocytes. Microscopic examination of the lungs revealed typical hemorrhagic infarcts. Many of the pulmonary vessels contained thrombi, and several of the thrombi showed canalization (fig. 6). Some of the bronchi and surrounding alveoli contained pus cells.

The diagnosis was: acute phlebitis and thrombosis of the external jugular vein, pulmonary thrombi and early bronchopneumonia.

Series 5.—Dog 1.—This dog, which weighed 9.6 Kg. before the experiment, died at the end of six days.

At autopsy, examination of the operative site in the region of the insertion of the steel needle revealed no evidence of infection. The wall of the external jugular vein was thickened. A thrombus extended from the traumatized portion of the vein distal to the site of the insertion of the needle (fig. 7). This thrombus was fragile and almost occluded the lumen of the vein. The lungs were riddled with hemorrhagic infarcts. A cross-section of the lung revealed many hemorrhagic infarcts, a few of which were triangular and had their bases directed peripherally.

Microscopic examination of the external jugular vein distal to the tip of the needle, shown in figure 7, revealed a thrombus attached to the wall of the vessel and partially occluding the lumen (fig. 8). A number of polymorphonuclear leukocytes were seen throughout the wall. Microscopic section of the lungs revealed typical hemorrhagic infarcts associated with pulmonary thrombi (fig. 9).

The diagnosis was: acute phlebitis and thrombosis of the external jugular vein and multiple pulmonary infarcts and thrombi.

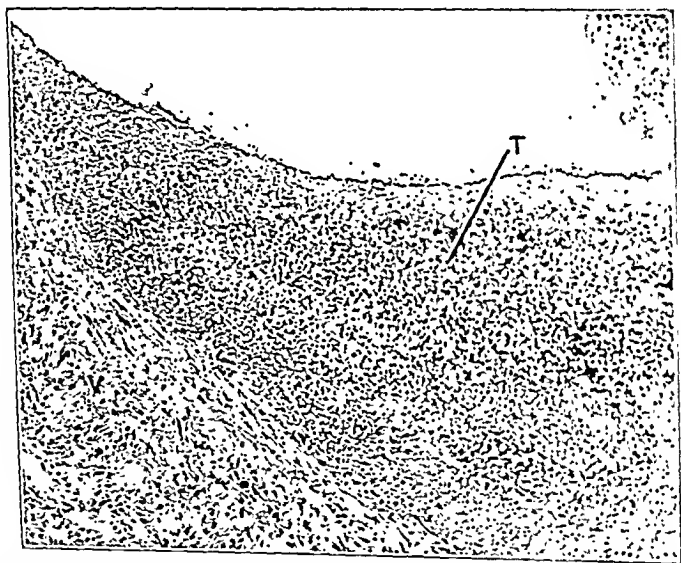


Fig. 8.—A photomicrograph of the external jugular vein of a dog at the site indicated in figure 7. The section was taken distal to the tip of the needle. Note the thrombus in the wall of the vessel.

Dog 2.—This dog, which weighed 11.6 Kg. before the experiment, was killed at the end of ten days.

The observations at autopsy were identical with those found in the dog in which the steel needle was inserted.

The diagnosis was: acute phlebitis and thrombosis of the external jugular vein and multiple pulmonary infarcts and thrombi.

Dog 3.—This dog, which weighed 9.2 Kg. before the experiment, was killed at the end of ten days.

The observations at autopsy were almost identical with those made on dogs 1 and 2 of this series.

The diagnosis was: acute phlebitis and thrombosis of the external jugular vein, multiple pulmonary infarcts and thrombi.





Fig. 9.—A photomicrograph of a section of the lung of a dog showing pulmonary thrombosis and infarction following the insertion of a steel needle in a jugular vein for six days.



Fig. 10.—A photomicrograph of a section of the lung of a dog at the end of six days. A thrombus had been released in one of the jugular veins. Note the thrombus in one of the pulmonary vessels.

*Series 6.*—Dog 1.—This dog, which weighed 8.7 Kg. before the experiment, was killed at the end of six days.

At autopsy examination of the lungs revealed crepitation throughout. No infarcts were seen or palpated. When cross-sections of the lungs were made no infarcts were found. Careful dissection of the pulmonary vessels, however, revealed a thrombus lodged in one of the larger pulmonary vessels.

Microscopic examination of the pulmonary thrombus revealed no organization and no surrounding infarcts (fig. 10). The lungs showed no edema or pneumonia.

The diagnosis was pulmonary thrombus.

Dog 2.—This dog, which weighed 9.5 Kg. before the experiment, was killed at the end of eight days.

The observations at autopsy were identical with those for the other dog on which the same experiment was tried.

The diagnosis was pulmonary thrombus.

#### SUMMARY AND CONCLUSIONS

A foreign body, such as a cannula, lodged in the vein of a dog produces an inflammatory reaction throughout the wall of the vein. All the necessary factors for thrombosis are present, namely: slowing and eddying of the blood current; trauma to the wall of the vessel, and changes in the composition of the blood. In all the animals used in the experiments there was an evident inflammatory reaction of the wall of the vein, with partial occlusion of the lumen by an organizing fragile thrombus. There is no difference in the reactions caused by the various types of commonly used cannulas, as demonstrated in these experiments. The results of the experiments indicate that a foreign body in a vein is more active in the production of thrombi than is the infused solution.

The animals used in the experiment lost weight while receiving solutions by venoclysis. A 10 per cent solution of dextrose given in the same quantity per body weight as it is given clinically to man does not provide enough nutrition to maintain body weight.

All dogs showed a high incidence of pulmonary infarction and thrombosis after having received venoclysis. The pulmonary infarcts usually were associated with other pulmonary pathologic changes, such as pneumonia and edema.

Well formed clots were injected into the external jugular veins of dogs having apparently normal lungs. At autopsy, pulmonary thrombi were found, but no pulmonary infarcts.

This experimental work shows that pulmonary complications such as bronchopneumonia and edema predispose to pulmonary infarction when thrombi are circulating in the pulmonary vessels.

By analogy it seems probable that pulmonary embolism and thrombosis are not infrequently associated with continuous venoclysis as used in man, although they may not always be recognizable clinically.

The experiments recorded here indicate that continuous intravenous infusions are not without danger.

# DIFFERENTIATION OF BENIGN AND MALIGNANT GASTRIC ULCERS

## UNRELIABILITY OF DIAGNOSTIC CRITERIA

ANDREW B. RIVERS, M.D.

Division of Medicine, the Mayo Clinic

AND

THOMAS J. DRY, M.B.

Fellow in Medicine, the Mayo Foundation

ROCHESTER, MINN.

No pathognomonic symptoms are invariably present in gastric carcinoma the recognition of which permits the early diagnosis of the disease. Often one witnesses the tragedy of a patient presenting himself for the first time with all of the evidences of a lesion which has progressed to a state of inoperability. In some cases, there were no warning symptoms of the disease; in others, the patient procrastinated because he attributed no importance to symptoms that might have served as the clue for an early diagnosis.

Much can be done toward remedying this situation by the systematic education of the laity, as is being done through the efforts of Dr. Bloodgood and of others who in lectures and through the press are cautioning the public against tolerating heedlessly the early and insidious manifestations of gastro-intestinal disease, especially of that occurring in persons past the age of 40. Needless to say, a responsive attitude on the part of the public imposes on the physician the added responsibility of discovering the malignant growth which otherwise may develop to an advanced stage "under his very nose." He may thus save himself the embarrassment of becoming a witness to the final stage of a malignant disease that has masqueraded under the guise of peptic ulcer or has been diagnosed as "nervous indigestion."

A sense of false security has developed among physicians regarding the benignity of certain types of gastric lesions for which they had advised nonsurgical treatment. Certain criteria for the benignity of gastric ulcer have been utilized in some instances to the advantage of the patient and for the cure of his disease. Altogether too frequently, however, the application of the same criteria has biased the judgment of the physician to the serious jeopardy of the patient's life. In many instances lesions which would have lent themselves to successful surgical treatment progress to the stage of inoperability because, during the time in which

---

Read before the Pan-American Medical Association, Pan-American Medical Floating Congress, March 14 to 31, 1934.

these lesions were easily resectable, the patients were subjected to medical regimens not sufficiently supervised to prove the benignity of the lesion. Indeed, the subjection of a patient with a gastric lesion to a nonsurgical form of treatment imposes an obligation which far surpasses that of the mere relief of the subjective manifestations of the disease and of the improvement in the general condition, since a carcinomatous gastric lesion may at times exhibit apparently favorable progress under the approved method of treatment for peptic ulcer.

The syndrome characteristic of peptic ulcer has been so thoroughly learned by medical practitioners that indigestion, with any of the characteristic symptoms of ulcer, often is assumed to be due to ulcer without the patient being given the benefit of roentgenologic examination. It is not possible by the history alone to distinguish between gastric and duodenal ulcer, and, whereas the latter is almost invariably benign, there is always a grave possibility that gastric ulcer may be malignant. It is therefore advisable to subject patients with any type of indigestion not immediately responsive to the ordinary conservative methods of treatment to a careful, systematic and thorough examination, which should include the study of the gastric contents, the examination of the stools for blood and a roentgenologic investigation of the stomach.

Errors of diagnosis, however, are not limited to those who neglect to examine the patient with sufficient thoroughness, because an ulcerating lesion in the stomach, even when demonstrated roentgenographically, has too often been assumed to be benign without sufficient corroborative evidence. It has been assumed that a long history of indigestion, high gastric acidity, situation of the ulcer high on the lesser curvature, demonstration of the ulcer as of the penetrating variety, the presence of an hour-glass deformity, early age of the patient and small size of the ulcer argue in favor of the benignity of the lesion. Yet all practitioners have been witnesses, sometimes too late, to the tragedy of the discovery that these signs were not reliably indicative of benignity.

Certain therapeutic tests have been developed the fulfilment of which theoretically is conclusive evidence of the benignity of the lesion. Thus, the fact that an ulcer becomes smaller or disappears under treatment, ceases to bleed or becomes quiescent has been assumed to stamp it as benign. Unfortunately, such tests are not always infallible.

Academically, it may be admitted that many signs are usually interpretative of the benignity of a lesion. However, since these signs are not absolutely reliable, it seems hazardous to employ them as criteria without due precautions.

In numerous instances multiple ulcerating lesions are present in the stomach, one of which is malignant. Attention may thus be focused on the lesions that are benign and are healing, whereas the one lesion, perhaps the smallest, may harbor within its periphery unmistakable evidence of malignancy.

It is obviously impossible to distinguish positively between malignant and benign lesions without a careful microscopic investigation. Direct inspection of an ulcer often fails to reveal signs which are even suggestive of carcinoma, and the lesion is assumed to be benign until the pathologist demonstrates its malignant nature by microscopic examination.

Duodenal and gastric ulcers are found to coexist in about 13 per cent of the cases. Not infrequently at the time a duodenal ulcer is discovered, further investigation of the stomach, either at fluoroscopic examination or at surgical exploration, is not executed with sufficient care, and a gastric ulcer may be thus overlooked. It is therefore essential, in dealing with cases of indigestion, to exercise every precaution in order to establish a complete diagnosis and to institute appropriate therapy.

The histories of several cases are presented here to demonstrate the unreliability, in certain instances, of practically every sign and symptom that has been employed to distinguish the benign from the malignant gastric ulcer.

Perforating ulcers are more likely to be benign, and ulcers accompanied by hour-glass deformity of the stomach are usually benign. According to Hurst and Stewart,<sup>1</sup> less than 1 per cent of the cases of hour-glass deformity of the stomach are due to carcinoma. In case 1 the patient was relatively young, the symptoms were characteristic of peptic ulcer and the gastric acidity was not low. Both in case 1 and in case 2 the character of the symptoms changed; such a change is often emphasized as suggestive of a malignant process. As a matter of fact one cannot be certain of arriving at the correct pathologic diagnosis on this basis alone, since a benign peptic ulcer manifests a similar change in symptoms when it extends into an adjacent viscus. The change simply indicates that the ulcer is no longer simple; it has become complicated, but with no implicit reference to malignancy. The same features are illustrated in case 2, with the exception that here the age of the patient makes one suspect the existence of a malignant process.

#### REPORT OF CASES

CASE 1.—A man, aged 36, had suffered from "stomach trouble" intermittently for six years. This complaint had consisted of a cramplike gnawing and burning associated with bloating and belching. Vomiting or the ingestion of food or of soda brought relief. During the five months prior to his admission to the clinic the pain had been more severe and had radiated to the back as well as upward into the thorax. The pain had awakened him during the night, but he had been able to sleep after taking soda. The stools had been dark at times. In two years the loss of weight had been only 13 pounds (5.9 Kg.).

---

1. Hurst, A. F., and Stewart, M. J.: *Gastric and Duodenal Ulcer*, New York. Oxford University Press, 1929, p. 342.

The report of the roentgenologic examination was: Perforating ulcer on the lesser curvature of the stomach with hour-glass deformity. Analysis of the gastric content revealed total acid of 60 and free hydrochloric acid of 40. The amount of gastric content recovered was 120 cc. At exploration a carcinomatous ulcer was found measuring 9 by 6 by 2.5 cm. It had perforated into the pancreas; glandular as well as serosal involvement was present. The pathologic diagnosis was carcinoma, grade 4.

CASE 2.—A woman, aged 58, had undergone appendectomy and drainage of the gallbladder eight years prior to admission to the clinic for the relief of burning epigastric pain which appeared from two to two and one-half hours after a meal. Following this operation there were no symptoms for a year; intermittent attacks of pain of a similar character then appeared, which were eased by the taking of food. The patient stated that during the five months previous to admission the pain had been replaced by bloating and marked belching until two weeks before her application to the clinic. At that time severe distress developed in the upper portion of the abdomen on the left side. Analysis of the gastric content revealed total acid of 60 and free hydrochloric acid of 40. The roentgenologic diagnosis was gastric ulcer located high in the stomach with the production of an hour-glass deformity. The clinical diagnosis was perforating gastric ulcer with hour-glass deformity of the stomach. At exploration a carcinomatous ulcer 3.5 cm. in diameter was found.

The next case to be reported is an excellent example of the type in which the pathologist unexpectedly finds carcinoma in an ulcer that has given no cause for the suspicion of malignancy in the mind of the clinician, of the roentgenologist or even of the surgeon at the time of the exploration. The history was characteristic of peptic ulcer. Relief had been obtained on a medical regimen for the treatment of ulcer, and the gastric acidity had been determined as adequate.

CASE 3.—A woman, aged 47, had for many years suffered from a burning pain which came on two or three hours after meals and was associated with attacks of migraine. Food and soda had relieved the distress. During the past year the trouble had been more severe; radiation of the pain to the back was associated with vomiting that came on at the height of the pain. Hospitalization for three months and a regimen for the treatment of ulcer had given complete relief as long as the patient remained on the diet. In two years she had lost only 4 pounds (1.8 Kg.). Analysis of the gastric content revealed total acid of 80 and free hydrochloric acid of 38. The roentgenologic examination disclosed an ulcer at the outlet of the stomach with resulting retention. The clinical diagnosis was ulcer at the pylorus with a slight obstruction. At operation, a lesion with a deep crater 2 cm. in diameter was found on the posterior wall above the pylorus. The pathologist reported a carcinomatous ulcer with glandular involvement.

The next case illustrates that even multiple lesions may occupy such positions in the stomach or the duodenum as to escape detection by an expert roentgenologist. Again it demonstrates the difficulty of recognizing a malignant process by macroscopic inspection. Unless great care is exercised by the surgeon, a duodenal ulcer may serve as a cloak for malignant gastric disease at the time of the exploration.

CASE 4.—A man, aged 46, had suffered intermittent attacks of epigastric pain, with relief by food and soda, for twenty-five years prior to his admission to the

clinic. During the past two years the pain had been more constant, and there had been distress at night. During the past few months food had relieved him less effectively than formerly. Two years prior to application at the clinic he had been on a milk diet with partial relief of the symptoms. He had lost 16 pounds (7.3 Kg.) during this period. Analysis of the gastric content revealed total acid of 88 and free hydrochloric acid of 58. The results of the roentgenologic examination were not significant. At operation two ulcers were found on the lesser curvature. A duodenal ulcer also was found. The pathologic report was: two gastric ulcers—the larger, carcinomatous; the smaller, benign.

The next case illustrates that a benign duodenal ulcer may coexist with a much graver lesion in the stomach. It is obvious that symptoms caused by the duodenal ulcer may entirely mask those produced by the ulcerating lesion in the stomach.

CASE 5.—A man, aged 42, for twenty years had complained of intermittent epigastric pain which appeared several hours after meals and was relieved by soda. During the past year he had not been troubled until one month prior to admission to the clinic, when the distress returned. Twelve days prior to admission he had a severe hemorrhage. He had lost 18 pounds (8.2 Kg.) in two months. Analysis of the gastric content revealed total acid of 58 and free hydrochloric acid of 38. The roentgenologic examination disclosed the presence both of gastric and of duodenal ulcers. At operation the roentgenologic diagnosis was verified, but the microscopic examination revealed the gastric ulcer to be malignant.

Severe gastric hemorrhage is much more liable to occur with a benign than with a malignant lesion. In the sixth case the bleeding was associated with symptoms characteristic of peptic ulcer. Dietary measures afforded relief of the symptoms, and the roentgenologic examination failed to reveal definite evidence of malignant disease, yet the surgeon discovered an inoperable carcinoma.

CASE 6.—A man, aged 46, had suffered from symptoms of ulcer during the spring and the autumn for about nine years. A diet for the treatment of gastric ulcer usually had relieved the symptoms during these attacks. For two or three years previous to admission the pain had been more severe and had radiated to the left lower quadrant of the abdomen, to the back and to the thorax. Four months prior to admission he had a severe hemorrhage, as a result of which he was confined to bed for seven weeks. Since that time he had been on a diet of milk and powders and was considerably improved. Roentgenologic examination revealed an ulcer on the posterior wall of the stomach. A clinical diagnosis of hemorrhagic gastric ulcer was made. At operation a carcinoma was found on the posterior wall, attached to the tail of the pancreas. The lesion was inoperable. A biopsy was made, and the pathologist reported the presence of carcinoma. The patient died one year later.

The next case so completely refutes the strictest criteria whereby the benign gastric ulcers may be distinguished from the malignant that the history is given in detail. Thus, if a patient with gastric ulcer, while under a strictly supervised medical regimen, becomes asymptomatic, if repeated tests reveal no blood in the stool and if there is roentgenologic

evidence of the complete disappearance of the lesion, there is assumed to be proof that the lesion is benign. The following case report demonstrates that this assumption is not always correct.

CASE 7.—A man, aged 28, complained of epigastric pain which had occurred at intervals during the five years prior to his admission to the clinic. The distress had come on from two to three hours after meals and had been relieved temporarily by food or alkalis. At times the pain had radiated to the thorax. Three years before, in 1928, a gastric ulcer had been suspected, but roentgenologic examinations by two physicians had given negative results. Appendectomy had been performed, and shortly afterward the gallbladder had been removed for the relief of the same symptoms. The distress, however, had continued. The pain had then been replaced by a feeling of gaseous distention. There was no history of melena at the time of the first visit to the clinic, in November 1931. Roentgenologic examination on Nov. 10, 1931, revealed a perforating ulcer on the lesser



Fig. 1 (case 7).—Roentgenographic appearance of the two ulcers occurring high on the lesser curvature of the stomach at the time of the first examination.

curvature above the angle of the stomach and a smaller ulcer slightly higher on the lesser curvature (fig. 1). Analysis of the gastric content revealed total acid of 46 and free hydrochloric acid of 38. The patient insisted on medical treatment; he was therefore hospitalized and placed on a strict regimen for the treatment of ulcer, which promptly relieved the symptoms. At times when he had epigastric distress, alkali afforded relief. Examination of the stools for the presence of blood on six occasions had given negative results. Roentgenologic examination was again made on November 18, and a small perforating lesion was seen to be still present on the lesser curvature; at a similar examination on November 24, the ulcer was found to be very shallow, and on December 2 it was no longer seen (fig. 2). Two days later the patient was dismissed from the hospital and returned to his home.

The trouble recurred shortly after the patient's dismissal, but during the subsequent winter he suffered little if any distress. In the spring and autumn, however, there was further epigastric distress, despite rigid adherence to the diet. During this period black stools were noted during several periods of three or



four days, and the patient's condition gradually became worse. The pain, although now localized, became more intense, "like molten lead," and was accompanied by a great deal of gas. Food and alkalis no longer afforded relief. The general condition of the patient remained good, and there was no loss of weight.

On the patient's return to the clinic in October 1932, roentgenologic examination revealed a large perforating ulcer high on the lesser curvature of the stomach and

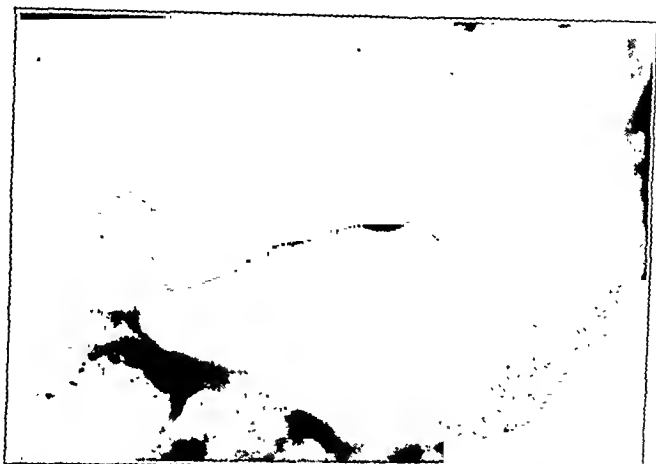


Fig. 2 (case 7).—Roentgenogram showing the disappearance of the gastric lesions seen in figure 1 following a course of medical treatment.



Fig. 3 (case 7).—Roentgenogram showing the recurrence of a perforating ulcer on the lesser curvature at the angle of the stomach and a smaller ulcer just above, about one year after the first examination.

a smaller ulcer immediately below the first (fig. 3). Malignancy was suspected, and at exploration a mass the size of a fist was found to involve practically the entire cardiac end of the stomach. Several large indurated glands were present in the area of lymphatic drainage. The patient died four months later. At necropsy the two gastric ulcers were proved to be malignant.

Just as at times it is difficult or impossible to exclude the presence of carcinoma, so a benign lesion may show characteristics with the hall-marks of malignancy. It is frequently assumed that lesions on the greater curvature are malignant. The files of the Mayo Clinic contain records of only four cases in which a lesion of the greater curvature proved to be benign. In the following case the presence of an epigastric mass, a lesion on the greater curvature, the persistence of blood in the stool, the absence of a history of ulcer and a loss of about 60 pounds (27.2 Kg.), even though the restriction of food had been serious, left no doubt in the minds of the clinicians and of the surgeons that the case was one of carcinoma of the stomach. It was assumed that the lesion could be resected, and exploration was advised. The ulcer was found to be benign and was resected without difficulty. Convalescence was without incident.

CASE 8.—A woman, aged 21, was admitted to the clinic in a state of serious malnutrition. Four and one-half years previously, she had begun to reduce her weight by self-imposed dietary restrictions and had appeased her appetite at times with little more than a candy bar. During this period she had worked hard at school and, despite the rather strictly limited intake of food, had retained reasonably good health until seven months prior to admission, at which time influenza had developed. Following this illness she had suffered from attacks of diarrhea which had caused a further reduction of weight, the total loss being about 62.5 pounds (28.3 Kg.).

The clinical picture, together with the history of semistarvation and diarrhea, was therefore one of marked inanition, and this condition seemed entirely adequate to explain the poor general condition. This opinion was further borne out by the fact that the proteins and calcium of the blood were reduced to 3.31 Gm. and 7.22 mg., respectively, per hundred cubic centimeters of serum. Edema was present in the feet, and the roentgenograms revealed osteoporosis of the pelvic bones. The patient gave no history of epigastric distress.

The immediate problem, therefore, resolved itself into a dietary program with the intake of foods high in calories and with an adequate supply of vitamins and food accessories. During this period repeated examinations of the stool for parasites and ova were made because of the history of diarrhea and were reported as giving negative results; it was noted, however, that several specimens contained occult blood. Subsequent examination in the hospital suggested an epigastric mass. After the patient's general condition was sufficiently improved to warrant further investigation, a roentgenologic examination of the stomach was made, which disclosed a large ulcerating lesion on the greater curvature that extended to the posterior wall of the stomach. The size of the ulcer and its situation on the greater curvature led the roentgenologist to suspect that it was malignant; this suspicion seemed warranted on the grounds of the roentgenologic evidence alone as well as on that of the presence of occult blood in the stool.

At exploration the surgeon found an ulcer on the greater curvature of the stomach, approximately 5 cm. above the pyloric sphincter. The crater of the ulcer, which admitted the tip of a finger, was 2 cm. in diameter. Pathologic examination of this ulcer and of enlarged glands proved that they were inflammatory; no evidence of malignancy could be found.

In the following cases definite indications existed that the lesions were malignant. In case 9, there was definite roentgenologic evidence of malignancy, and the analysis of the gastric content revealed absence of free hydrochloric acid.

CASE 9.—A man, aged 41, had for ten years complained of a burning pain in the upper part of the abdomen which came on from three to four hours after meals and was relieved by vomiting. One and one-half years prior to admission to the clinic he had an attack of vomiting lasting eighteen weeks. He had been placed on a regimen for the management of ulcer which had resulted in freedom from the trouble for about ten months. Four months before coming to the clinic there had been severe hematemesis and melena followed by intermittent distress and vomiting. Analysis of the gastric contents revealed total acid of 20 with no free hydrochloric acid. Roentgenologic examination disclosed an apparently inoperable lesion at the pyloric end of the stomach which was strongly suspected to be carcinoma. At operation a simple hemorrhagic ulcer, 1.5 cm. in diameter, was found. Eleven months after operation the patient was free from symptoms.

In case 10, the age of the patient was well within the range in which carcinoma is most prevalent, and there was a history of a loss of from 40 to 50 pounds (from 18 to 22.7 Kg.), the onset of which preceded the gastric symptoms by six or seven months. Further, the roentgenologic evidence was somewhat suggestive of a malignant growth. The clinician's diagnosis was carcinoma, but at operation a benign lesion was found.

CASE 10.—A man, aged 51, complained chiefly of aching pain over the lower mediastinum, which had no relation to meals or to exertion and which lasted for two or three hours. He had lost from 40 to 50 pounds during the year previous to admission to the clinic. Analysis of the gastric content revealed total acid of 58 and free hydrochloric acid of 46. Roentgenologic examination disclosed a lesion of the pyloric end of the stomach with a marked narrowing of the pylorus and the indication of a gastric ulcer on the lesser curvature. A clinical diagnosis of carcinoma of the stomach was made. At operation a subacute gastric ulcer perforating into the gastrohepatic omentum was found. Tissue removed for examination was found to be inflammatory.

The syndrome presented in case 11 was also suggestive of a malignant process. The patient was of the age at which carcinoma is most frequent, there was a family history of carcinoma, the history of the symptoms was short, the gastric acidity was low and the roentgenologic findings favored the suspicion of a malignant process. Here, again, the patient was proved to have a benign peptic ulcer.

CASE 11.—A man, aged 49, applied at the clinic for examination, with the complaint of hematemesis of the "coffee-ground" type and melena occurring one and one-half years prior to admission. His mother had died of "cancer of the liver." The patient had no pain or dyspepsia. Seven months after the first hematemesis a similar hemorrhage had occurred, since which time diffuse epigastric and abdominal pain had appeared from one to two hours after meals. This dis-

trass was usually relieved by soda. At times, however, the pain had been constant for days. The symptoms had become definitely worse two months prior to admission, and occasional vomiting had occurred. The loss of weight was 4 pounds (1.8 Kg.). Analysis of the gastric contents revealed in the first specimen total acid of 20 with no free hydrochloric acid, and in a second specimen, total acid of 24 and free hydrochloric acid of 4. The roentgenologic diagnosis was that of ulcerating carcinoma of the stomach. On exploration a large gastric ulcer on the lesser curvature was found. There were enlarged glands in the gastro-hepatic omentum and a circumscribed nodule in the liver. Microscopic examination proved the ulcer to be benign and the enlarged tissue of the glands to be inflammatory, whereas the nodule in the liver was revealed as a benign encapsulated tumor.

#### COMMENT

We have carefully reviewed the histories of two hundred patients with surgically verified gastric ulcers. Of this series of ulcers, one hundred were benign and one hundred malignant. The cases were taken in consecutive order except that preference was given to those in which before operation there was some doubt regarding the benignity or the malignancy of the lesion. Frank cases of carcinoma with abdominal masses or with evidence of metastasis and large lesions with unmistakable roentgenologic evidence of carcinoma were not selected for study. The histories of the cases were then summarized according to a uniform plan, and the summaries placed in one book, so that they could be easily reviewed. At the bottom of each page were the final diagnosis and the results of the surgical measures. From a review of all of the data available in the history an effort was made to determine the character of the lesion. It was surprising how frequently errors in diagnosis resulted.

The diagnosis of an intrinsic gastric lesion as a causative factor in the production of indigestion is made by analysis of the history, by the physical examination, by the investigation of the gastric content and the stool and by roentgenologic study. By careful evaluation of all of the data made available by these methods, the arrival at a diagnosis either of carcinoma or of ulcer is usually not at all difficult. The difficulty arises, however, when an attempt is made to differentiate between a malignant and a benign lesion when the lesion is small and has the roentgenologic appearance of ulcer. A careful evaluation of all of the information available in the histories corroborates the opinion that there are features which suggest the malignancy of certain lesions. Patients with gastric ulcers who have short histories and who have shown no remissions of symptoms, inadequate relief on medical regimens and persistent blood in the stool should be suspected of harboring malignant ulcers. If, in addition, the ulcer is large and is situated near the pylorus on the greater curvature or on the anterior wall and if hydrochloric acid in the gastric content is demonstrably

absent or diminished the probability that the lesion is malignant is great. If, on the other hand, the patient is young, if there are long periods during which the ulcer is quiescent, if the values for gastric acids are high, if bleeding from the lesion is intermittent, if the ulcer exhibits the characteristics of penetration or if the complication of hour-glass contracture is present, the probability of benignity is suggested. Further, clinical improvement under treatment, cessation of bleeding from the ulcer and roentgenologic evidence of the disappearance of the lesion add evidence that the lesion is benign. However, any one sign may fail in so many instances that it seems extremely hazardous to venture positive opinions regarding the exact histopathologic type of these small ulcers.

Bloomfield<sup>2</sup> stated that in most instances of carcinoma the gastric acids are reduced or absent and the total secretory volume is diminished. Evidently he was considering chiefly the larger lesions of the stomach, although occasionally even for small carcinomatous ulcers the assumption still holds good, and it may thus be of value in the differentiation of benign and malignant gastric ulcer. However, in cases of small malignant ulcer the results of the analysis of the gastric content frequently do not seem to be different from those usually obtained in cases of benign gastric ulcer. The possibility of correct diagnosis is further confused at times by the presence of multiple lesions. Occasionally, a malignant gastric ulcer is associated with a benign duodenal ulcer. In other cases in which there are multiple gastric ulcers, one may be malignant and the others benign.

It soon becomes evident that from the clinical history, particularly from the behavior of pain, not much help is available in the differentiation of benign and malignant lesions. This fact becomes evident when the mechanism for the production of symptoms in these lesions is considered.

The cause of distress in cases of benign and in those of malignant gastric ulcer should be the same. Gastric ulcer asserts its presence mainly over three nerve routes: the phrenic nerves, particularly if the lesion is high; the splanchnic branches of the sympathetic nervous system, and the afferent spinal sensory nerves. If the gastric lesion invades that portion of the diaphragm supplied by the phrenic nerves, the fact may be indicated by pain in the area of the peripheral cutaneous distribution of this nerve, that is, at the base of the neck or on the shoulder.

The second pathway by which the presence of a gastric ulcer is indicated is the splanchnic route. There seems to be no doubt at present that impulses interpretable as pain are conducted over fibers running

---

2. Bloomfield, A. L.: *Clinical Aspects of Gastric Secretion*, *Ann. Int. Med.* 6:307 (Sept.) 1932.

in the splanchnic nerves to the posterior horn. It is known, of course, that stimuli, such as pinching or cutting, which produce pain on the surfaces of the body do not usually produce pain in the viscera. Since it is known that pain actually develops when a lesion invades a viscus, it remains only to be ascertained what constitutes the stimulus that is adequate to produce the pain. It has been assumed, therefore, on good evidence that stretching of the circular fibers of the viscus constitutes an adequate stimulus. This, it has been suggested, is caused by a local accentuation of intravisceral tension. One of the factors that seems capable of producing the spasm is gastric acidity. We have frequently noted in the review of the cases included in this study that normal or elevated values for free hydrochloric acid were present in cases of malignant gastric ulcer. Furthermore, in many of this group of cases benign ulcers produced symptoms characteristic of the ulcer syndrome and yet the acidity, even after the use of stimulating test meals, was not elevated.

We see no good reason why this mechanism for the production of pain should be influenced in a different manner by a malignant than by a benign ulcer, unless marked differences in the gastric chemism are present. The low values for free hydrochloric acid are more consistently in evidence in cases of malignant ulcer, and although they may somewhat influence symptoms, they do not occur with sufficient regularity to be of conclusive diagnostic value.

Pain impulses from gastric ulcers may also reach the spinal cord by way of the spinal afferent sensory nerve tracts. The parietal peritoneum receives branches from the spinal sensory nerves. The gastro-hepatic omentum and the mesentery of the small intestine as well as the transverse mesocolon are also supplied by somatic nerves. These nerves are sensitive to the same stimuli that produce pain when applied to the surfaces of the body.

When ulcers, therefore, progress beyond the confines of the bowel in the course of perforation they invade tissues guarded by spinal sensory nerves. Pain may then be projected over the peripheral distribution of the involved nerves, and the original syndrome be thus appreciably changed. Frequently after the development of this complication, the previously established syndrome is markedly distorted. The tendency toward remission is lessened, pain is more persistent and severe and the usually effective methods of obtaining relief become entirely inadequate for the control of symptoms. Such a change in symptoms is often assumed to be evidence of the malignancy of a lesion, when in reality the alteration is quite as likely to happen in cases of benign as in those of malignant gastric ulcer.

Physical examination in cases of early gastric carcinoma is of little, if any, aid in diagnosis, since the findings which usually stamp the

lesion as malignant are the results of metastasis, such as enlarged supraclavicular glands or implants in the pouch of Douglas. Similarly, an epigastric mass usually signifies malignant disease with extension to the liver. It is precisely in the type of case in which the differential diagnosis is difficult, that is, in which a small ulcer is present, that physical signs are lacking. Neither the malignant nor the benign ulcer is likely to be associated with a mass. When in addition to the roentgenologic evidence of a small perforating ulcer a mass is demonstrable, it may just as readily be the result of an inflammatory reaction surrounding the ulcer as that of a malignant process.

Whatever doubt may exist is usually dispersed by a reliable roentgenologic examination, and the majority of carcinomas afford incontrovertible evidence of their malignancy when subjected to this means of investigation. But, unfortunately, the fact must again be faced that the most easily recognizable gastric carcinomas have too often progressed to an inoperable stage. Kirklin and Weber<sup>3</sup> emphasized the difficulty of determining exactly the morbid anatomy of small lesions of the stomach. They stated:

Most of the roentgenologic literature and illustrations of gastric carcinoma pertain to the advanced and essentially tumefactive growths, and tend to create the impression that both the discovery and the specific diagnosis of carcinoma are uniformly easy. However, this optimistic view is not warranted, for it takes no account of small malignant lesions, which are sometimes hard to reveal and more often hard to identify. . . . A crater which has not penetrated beyond the normal confines of the gastric lumen, and which is surrounded by an elevated, overhanging ridge, is pathognomonic of ulcerating carcinoma. On the other hand, when ulceration so dominates the morphology that no hyperplasia is evident, and the lesion is essentially and solely an ulcer excavating the gastric wall, distinction from benign ulcer may be difficult or impossible.

Data obtainable from the history, the analysis of the gastric content, the examination of the stool, the physical examination and the roentgenologic study are usually adequate for the correct diagnosis of carcinoma of the stomach. The application of all of the available evidence obtained by these means, however, fails in many instances to give satisfactory assurance of benignancy in some of the smaller ulcerating lesions of the stomach.

#### SUMMARY

Gastric ulcer is much more frequently benign than malignant. No infallible means except microscopic investigation can be applied to prove the benignity of the lesion under consideration. The histories of the cases included in this study amply illustrate that practically all of the signs and symptoms may at times fail to indicate the exact nature

---

3. Kirklin, B. R., and Weber, H. M.: Roentgenologic Diagnosis of Neoplastic Diseases of the Stomach, *Am. J. Cancer* 16:1134 (Sept.) 1932.

of the lesion. The symptoms of benign and those of malignant ulcer may be identical, and certain reasons for their similarity have been outlined.

We do not intend to convey the impression that the differentiation of benign and malignant ulcers of the stomach is impossible, for as a rule a correct diagnosis can be made. We do wish to imply, however, that it is hazardous to assume that the application of certain criteria of benignancy rules out the possibility of malignancy. It seems to us that unless contraindications are present it is usually safer to treat gastric ulcers surgically.

Nonsurgical methods of treatment should be undertaken only when it is possible to keep the patient under the closest observation for a prolonged period.



# FIFTY-SIXTH REPORT OF 'PROGRESS IN ORTHOPEDIC SURGERY

JOHN G. KUHNS, M.D.

EDWIN F. CAVE, M.D.

SUMNER M. ROBERTS, M.D.

AND

JOSEPH S. BARR, M.D.

BOSTON

JOSEPH A. FREIBERG, M.D.

CINCINNATI

JOSEPH E. MILGRAM, M.D.

NEW YORK

AND

ROBERT I. STIRLING, F.R.C.S. (EDIN.)

EDINBURGH, SCOTLAND

## CONGENITAL DEFORMITIES AND DISTURBANCES OF GROWTH

*Congenital Torticollis.*—Hough<sup>1</sup> gave a thorough summary of the possible causes, pathologic changes, symptomatology and treatment of congenital torticollis. Basing his statement on a review of 57 cases he stated that frequently in infants the condition responded to manipulation if treatment was instituted early but that for the older patients surgical intervention, i. e., division of either end of the sternocleidomastoid muscle, was necessary and should be followed by the wearing of some form of apparatus to maintain correction. Facial asymmetry usually disappeared within six months after the operation. Full active and passive correction was obtained in the 57 cases.

*Klippel-Feil Syndrome; Congenital Webbed Neck.*—From the clinical examination of 6 patients with the Klippel-Feil syndrome and the postmortem examination of 2 of these, Mitchell<sup>2</sup> concluded that the conception that the cervical region of the spine is absent in this condition is not exact. The normal number of intervertebral foramina and cervical nerves were present. There were, however, distortion and absence of portions of the intervertebral disks, bodies, etc. In later life there was a more or less complete fusion of the portions which were

---

This report is based on a review of 182 articles selected from 272 titles appearing in medical publications approximately between July 1 and Nov. 2, 1934. Only those which seemed to represent progress were chosen for review.

1. Hough, G. deN.: Surg., Gynec. & Obst. 58:972, 1934.

2. Mitchell, H. S.: Arch. Dis. Childhood 9:213, 1934.

present. Mitchell expressed the belief that there is usually a large exposed portion of the spinal cord and its membranes in the upper cervical region. This is not a true but a false spina bifida, since the arches meet in an abnormally low situation.

*End-Results of Coxa Plana as Related to Treatment.*—Caldwell<sup>3</sup> in reporting on the treatment of coxa plana stated that the available statistics showed that 1 of every 5 of the patients had a residual limp, pain and some restriction of motion in the hip joint. Five cases were reviewed as to the end-results. Three patients, aged 26, 38 and 18, had received no treatment, and 2, aged 20 and 22, had been given treatment, 1 with a caliper brace and 1 with a plaster spica. Nine other cases in which the patients were too young to warrant a definite statement as to the end-results were discussed. Caldwell concluded that the use of a caliper brace which partially relieves weight bearing is of value, particularly when acute symptoms are present, and that absolute immobilization in plaster is not indicated.

*Treatment of Legg-Calvé-Perthes Disease Without Weight Bearing.*—Danforth<sup>4</sup> observed the results of treatment in 6 cases of coxa plana and showed in 5 of them the great value of abstinence from weight bearing during the active stages of the disease. Three patients were treated by rest in bed for from three to four years; 2 were observed after twelve years, during three of which weight bearing was prohibited. All these patient had excellent results clinically, and the roentgenograms showed almost normal conditions. In the sixth patient, who did not follow advice as to abstinence from weight bearing, the result was much less satisfactory clinically, and the roentgenogram showed a deformed femoral head.

[ED. NOTE.—These studies of end-results suggest that prevailing theories regarding the nature and treatment of coxa plana will have to be modified. Abstinence from weight bearing should be the treatment until the roentgenograms disclose evidence of healing.]

*Adolescent Kyphosis.*—Edelstein<sup>5</sup> reported 8 cases of kyphosis in adolescent boys and girls and discussed the roentgen appearance and etiology of that condition. He concluded that most, if not all, of the etiologic factors usually cited to explain this and other epiphyseal disturbances of a similar nature are of only secondary significance. He suggested that some biochemical disturbance, based possibly on a defect of nutrition or assimilation, is at the root of such epiphyseal disorders.

3. Caldwell, G. A.: South. Med. J. 27:402, 1934.

4. Danforth, M. S.: J. Bone & Joint Surg. 16:516, 1934.

5. Edelstein, J. M.: Brit. J. Surg. 22:119, 1934.

## PYOGENIC INFECTIONS

*Osteomyelitis of the Ilium.*—Osteomyelitis of the ilium, as was pointed out by Badgley,<sup>6</sup> is not as infrequent as is usually believed. Probably 1 or 2 per cent of all the patients with osteomyelitis showed involvement of the ilium. The age incidence in his series of 24 cases varied from 20 months to 75 years; the usual age was under 25 years. Badgley carefully reviewed the literature on the subject and discussed the development of the pelvis and its anatomic structure in relation to osteomyelitis. The etiologic agent was predominantly *Staphylococcus aureus*. Badgley discussed in detail the signs, symptoms and roentgen appearance. Pain was most often referred to Scarpa's triangle. The treatment varied depending on whether the case was acute, subacute or chronic. In the acute stage, if the process is localized incision and drainage with eradication of the involved bone are advisable. If the process is diffuse, either with or without abscess formation, Badgley recommended radical subperiosteal resection of the ilium as soon as the patient's general condition warrants it. He expressed the belief that acute diffuse osteomyelitis should not be treated by simple incision and drainage or by trephination. When septicemia is present the prognosis is grave, but radical resection gives the best chance of recovery. In the subacute stage localized osteomyelitis should be treated by local resection, and the diffuse type, by radical resection of both tables of the ilium including all the diseased bone if possible. As treatment for the chronic stage Badgley advised resection of both tables of the ilium and saucerization of the cavity. The operative exposure which he used was described in detail. It consisted in an incision along the iliac crest from the posterior to the anterior superior part of the spine and then continued downward lateral to the sartorius muscle. The wing of the ilium was exposed by subperiosteal dissection of the inner and outer tables. Resection of whatever portion of the ilium was necessary was then easily made with the osteotome. The wound was packed with gauze smeared with petrolatum. Seventeen of the 24 patients were considered completely cured.

*Treatment of Acute Infective Arthritis of the Knee Joint.*—Monat<sup>7</sup> drew attention to the fact that in acute infective arthritis of the knee joint there is frequently an extension abscess passing from the sub-crureus pouch up in front of the femur deep to the quadriceps extensor muscle. To drain this abscess he advocated that the lateral incision for drainage of the joint be extended upward, cutting through the vastus lateralis muscle down to the femur.

6. Badgley, C. E.: *Osteomyelitis of the Ilium*, Arch. Surg. 28:83 (Jan.) 1934.

7. Monat, T. B.: Brit. M. J. 1:980, 1934.

*Suppurative Infections of Bones and Joints in Infancy.*—After reviewing the end-results of sepsis involving the bones and joints in infants (up to 2 years) at the Children's Hospital, Boston, Green<sup>8</sup> concluded that early operation for drainage is of most value in cases of septic joints. Osteomyelitis, however, responds best to conservative early treatment laying stress on general supportive measures. After the process has been localized it should be drained by a small window in the bone; extensive destructive operations should be avoided. Green stressed the importance of the choice of the proper time for operative intervention and the necessity of improving the infant's general condition by an adequate intake of fluid, etc., to lower the otherwise high mortality in this group of cases.

#### POLIOMYELITIS

*Polioomyelitis Treated with the Drinker Respirator: Analysis of 88 Cases and 68 Control Cases.*—In the epidemic of anterior poliomyelitis in New York in 1931, Landon<sup>9</sup> was able to study a group of 88 patients treated in the Drinker respirator and a control group of 68 patients with equally serious respiratory embarrassment for whom no respirators were available. All were treated in four hospitals for communicable diseases in New York. Of the 88 patients treated in the respirator 11 were moribund on admission, and 53 died in the hospital. Of the 68 treated without respirators 40 died in the hospital. Most of the deaths occurred on or before the sixth day after the onset of paralysis; the percentage of deaths was 66 per cent for those treated in the respirator and 65 per cent for those treated without the respirator. Thirty-five patients who were treated in the respirator were discharged from the hospital free from respiratory embarrassment. Of these, 16 died within eighteen months, chiefly from pneumonia. Twenty-eight patients treated without the respirator and discharged when free from difficulty in breathing were followed for eighteen months; 3 of these died. Post-mortem examination of the patients coming to autopsy showed alveolar emphysema in those treated in the Drinker respirator. Landon expressed a belief that hyperexpansion of the lungs may predispose patients treated in the respirator to subsequent infection or collapse. The Drinker respirator was not found to be of value in cases of bulbar paralysis. Landon suggested that the usefulness of the Drinker respirator is established only in selected cases of diaphragmatic and intercostal paralysis.

[ED. NOTE.—The careful study made by Landon is salutary in the face of the enthusiastic acceptance of respirators for the treatment of

8. Green, W. T.: New England J. Med. 211:159, 1934.

9. Landon, J. F.: J. Pediat. 5:1, 1934.

poliomyelitis associated with thoracic and diaphragmatic paralyses. It suggests that a more careful selection be made of the patients on whom such treatment is attempted.]

#### TUBERCULOSIS

*Surgical Tuberculosis: Its Treatment by Climate and Sunlight During Forty-Seven Years.*—Bernhard<sup>10</sup> wrote an enthusiastic article in favor of heliotherapy in high altitudes for all types of tuberculosis. He has treated about 2,500 patients with "surgical tuberculosis" in the past forty-seven years. He reported the following statistics on the first 1,000 patients: cured, 858; improved, 120; unimproved, 14; dead, 8 (0.7 per cent). Of the unimproved patients, 6 died later of tuberculosis. Bernhard stressed the climatodietetic therapy, consisting of high altitude, nourishing food and maximal periods of direct exposure to the sun. In cases of tuberculosis of the bones and joints, although no statistics or illustrations were given, he reported complete healing with frequent regeneration of the bones and excellent function of the affected joints.

[ED. NOTE.—This article, written by one of the pioneers in heliotherapy, overflows with enthusiasm and conviction. Nevertheless, some of the statements as to results could be accepted more readily if statistics and roentgenograms were included.]

*Functional Test of the Reticulo-Endothelial System with Congo Red for Qualitative Diagnosis of Osteo-Articular Tuberculosis.*—Rabboni and Alberghina<sup>11</sup> injected 1 cc. of a 1 per cent solution of congo red per six kilograms of body weight intravenously into one arm of patients with tuberculous joints. After one hour 5 cc. of blood was withdrawn from the other arm. By colorimetric tests on normal persons 100 per cent of the dye was noted in the plasma. Rabboni and Alberghina believed that the percentage of reduction in color indicated the type and severity of the lesion. The percentage of color noted in various cases varies from 50 to 95. The higher the percentage of color in the plasma, the more favorable the prognosis. The writers stated that others had used the test with congo red for pulmonary tuberculosis.

[ED. NOTE.—This test, which is really a check on the functional activity of the reticulo-endothelial system, has been used for amyloid disease. Its value can be of only relative significance in tuberculous infections.]

#### CHRONIC ARTHRITIS

*Gonococcus Complement-Fixation Test in Blood and Synovial Fluid of Patients with Arthritis.*—Myers and Keefer<sup>12</sup> determined the gono-

10. Bernhard, O.: Arch. Phys. Therapy 15:261, 1934.

11. Rabboni, F., and Alberghina, G.: Chir. d. org. di movimento 18:599, 1933.

12. Myers, W. K., and Keefer, C. S.: New England J. Med. 211:101, 1934.

coccus complement-fixation test in the blood, synovial fluid or both of 120 patients with arthritis. In 43 of these the condition was diagnosed as gonorrheal arthritis, the diagnosis being based on the following criteria: (1) a history of a recent attack of gonorrhea, (2) a localized gonorrheal infection in the genital tract and (3) the presence of gonococci in the synovial fluid. In 37 of the 43 cases diagnosed as instances of gonorrheal arthritis the gonococcus complement-fixation test gave positive results. In only 2 of the 71 patients with various other forms of arthritis did the gonococcus complement-fixation test give positive results. The reactions in the blood serum and synovial fluid were identical except in 6 instances. Determination of the reactions of the synovial fluid gave no definite information not obtainable from a study of the blood serum. Myers and Keefer expressed the belief that the test is of considerable significance in the differential diagnosis of arthritis.

*Characteristics of Synovial Fluid in Gonococcic Arthritis.*—Myers and his co-workers<sup>13</sup> studied 40 cases of gonococcic arthritis. In 25 per cent (10 cases) the organism was recovered in direct smears or culture of the fluid. The complement-fixation test of fluid from the joint was positive in 71 per cent of the cases studied. In only 6 instances was there disagreement in the results of the test of the blood and of the fluid from the joint. The cell count of the synovial fluid ranged from 1,800 to 158,000 per cubic millimeter. In general the higher cell counts were found in fluids with a culture positive for gonococci. The polymorphonuclear leukocytes constituted from 46 to 100 per cent of the total cell count. The chemical analysis (total protein and sugar content) was of little value. In all the cases the prognosis for complete recovery was poor. Patients with infected fluid and high leukocytic counts were more often crippled than the others.

[ED. NOTE.—The two papers by Myers and his co-workers add to the diagnostic methods for chronic arthritis. In the experience of one of us, gonorrheal arthritis once it has become chronic behaves like chronic rheumatoid arthritis. A note of warning should be raised in regard to a positive gonococcus complement fixation; it is possible to have an incidental gonorrheal infection, as has been observed, without any direct bearing on the course of chronic arthritis.]

*Symmetrical Serous Synovitis (Clutton's Joints).*—Sixty-three cases of bilateral serous synovitis in patients with congenital syphilis were reported by Klauder and Robertson.<sup>14</sup> The onset was insidious and practically without symptoms. The joints were painless, and there was

13. Myers, W. K.; Keefer, C. S., and Holmes, W. F.: J. Clin. Investigation **13**:767, 1934.

14. Klauder, J. V., and Robertson, H. F.: Symmetrical Serous Synovitis (Clutton's Joints), J. A. M. A. **103**:236 (July 28) 1934.

no bony involvement. The disease was chronic and ended in eventual spontaneous recovery. The response to antisyphilitic treatment was slow, but the treatment probably influenced recovery to some extent. The age and sex incidence corresponded closely to those of interstitial keratitis, with which Clutton's joints were frequently associated, and to those of Hutchinson's teeth. Klauder and Robertson expressed the belief that Clutton's joints are an important sign of congenital syphilis and one frequently overlooked in this country.

#### NEOPLASMS

*Lymphosarcoma in Bone.*—Craver and Copeland<sup>15</sup> reviewed the records of 164 patients with lymphosarcoma who were treated at the Memorial Hospital for the Treatment of Cancer and Allied Diseases in New York. Seventeen of these were found to have metastases to bone, the diagnosis of osseous metastases being made during life in all. The bones most commonly involved were, in order of frequency, the spine, pelvis, skull and femur. In 5 patients pathologic fractures occurred. The metastatic lesions were commonly osteolytic, although osteoplastic and combined osteoplastic and osteolytic lesions were seen. The extension of the neoplasm was either by the blood stream or by direct infiltration from involved lymph nodes. Histologic study of the metastases in all cases showed reticulum cell lymphosarcoma. The lymph nodes were involved in all cases before bony metastases occurred.

*Skeletal Muscle Sarcoma.*—Of 35 cases of tumor of the skeletal muscle collected by Bick<sup>16</sup> from the records of the Hospital for Joint Diseases and the Mount Sinai Hospital there were 20 cases of sarcoma and 11 of hemangioma. Sarcoma was found to occur on an average in patients from 20 to 40 years of age. The duration in all but 1 case was a year or less. The common sites were the thigh, abdominal wall and forearm. The tumors were usually mobile and, of course, moved with muscular contraction and relaxation. Pain was not a common symptom. Bick expressed the belief that treatment should consist of wide excision.

*Changes in the Bone in Hodgkin's Granuloma.*—Craver and Copeland<sup>17</sup> reported observations on 172 cases of Hodgkin's granuloma in which autopsy was performed at the Memorial Hospital for Cancer and Allied Diseases in New York. Osseous changes should be expected at any time during the course of the disease. Such changes were due to

---

15. Craver, L. F., and Copeland, M. M.: *Lymphosarcoma in Bone*, Arch. Surg. 28:809 (May) 1934.

16. Bick, E. M.: Ann. Surg. 99:949, 1934.

17. Craver, L. F., and Copeland, M. M.: *Changes in the Bone in Hodgkin's Granuloma*, Arch. Surg. 28:1062 (June) 1934.

metastasis from the bone marrow or to direct extension from glands. The spine and pelvis were most frequently involved. Collapses of vertebrae, but not involvement of the intervertebral disks, were common, but pathologic fractures were rare. Craver and Copeland concluded that of all forms of treatment advocated, irradiation was the best.

#### MUSCULAR INJURIES

*The Common Syndrome of Rupture, Dislocation and Elongation of the Long Head of the Biceps Brachii Muscle.*—The symptom complex of rupture of the long head of the biceps brachii muscle is not as rare as was formerly supposed. In addition, there are cases of partial rupture, dislocation and elongation of the tendon. In an excellently written article Gilcreest<sup>18</sup> considered the anatomy, pathology, signs, symptoms and treatment of these conditions and presented an analysis of 100 cases. He recommended open repair and suture as the treatment of choice.

*Appearance of Bone Formation About the Elbow Joint.*—During a period of five years 930 gymnasts and athletes were examined with roentgen rays by Heiss.<sup>19</sup> In 30 per cent abnormal bony formation was found about the elbow. Some of these athletes had had severe injuries or dislocations; others had suffered no such injuries. In this group osseous bodies were found about the median epicondyle, the olecranon, the coracoid, the edge of the trochlea and the ulnar articulation. Heiss attributed these growths to unusual strains and stresses occurring in sports.

#### DISABILITIES OF THE KNEE JOINT

*Cysts of the External Cartilage of the Knee with Erosion of the Head of the Tibia.*—Two cases of cysts of the lateral meniscus causing erosion of the lateral condyle of the tibia were reported by Fairbank and Lloyd.<sup>20</sup> In both cases there were multiple cysts, and in one the erosion in the tibia was 1¼ inches (3.18 cm.) in length and 1 inch (2.54 cm.) in depth. Removal of the cystic mass and part of the meniscus was carried out in both cases, and the subsequent course was satisfactory.

#### MISCELLANEOUS CONDITIONS

*Calcification, Decalcification and Ossification.*—Jones and Roberts<sup>21</sup> correlated the pathologic, biochemical, clinical and roentgenologic features of normal and abnormal calcification, decalcification and ossification on the basis of the theories of Leriche and Policard. They

18. Gilcreest, E. L.: Surg., Gynec. & Obst. 58:322, 1934.

19. Heiss, F. D.: Deutsche Ztschr. f. Chir. 242:342, 1934.

20. Fairbank, H. A. T., and Lloyd, E. I.: Brit. J. Surg. 22:115, 1934.

21. Jones, R. W., and Roberts, R. E.: Brit. J. Radiol. 7:321 and 391, 1934.



expressed the belief that bone undergoes decalcification if the blood supply is increased and shows increased calcification if the blood supply is diminished. They considered that from a pathologic standpoint calcification is possible in any mesenchymatous tissue of low metabolism where the vascularity is reduced by the fibrosis of trauma or of infection. Bone can form in any region where there are fibroblasts, excess of calcium and an adequate blood supply.

*Habitual Adduction and Supination Distortions of the Foot.*—Dehne<sup>22</sup> mentioned that in sprains of the foot the anterior and occasionally the posterior talofibular ligament are ruptured. In such cases the prognosis is favorable only if complete healing of the ligaments occurs. The appearance of the roentgenograms suggests instability of the astragalus. This instability causes abnormal movement of the astragalus and is frequently the cause of pain in chronic foot strain. Dehne found that repair of the torn ligaments is quite slow. After six weeks of immobilization in a plaster bandage not a single patient had regained normal ligamentous length. Secondary contraction of the ligaments began after the second month and sometimes required a year for completion. The author advised the use of adhesive plaster in severe cases. It is necessary to maintain support for from two to four months to ensure proper shrinkage and repair.

#### ORTHOPEDIC OPERATIONS

*Mixed Intra-Articular and Extra-Articular Arthrodesis of the Shoulder in Poliomyelitis.*—Scaglietti<sup>23</sup> described a combined intra-articular and extra-articular fusion of the shoulder joint for paralysis of the shoulders. By means of an incision through the deltoid muscle the shoulder joint is opened, and the humeral head is dislocated. The articular cartilage is removed from the humeral head and the glenoid; the dislocation is reduced and the capsule sutured. Incision is then extended from the tip of the acromion backward along the scapular spine, from which a long osteoperiosteal graft is removed. The graft is rotated 180 degrees and the distal end is buried under a flap of bone in the greater tuberosity of the humerus. The graft is held in place in a channel in the acromion by periosteal sutures. A spica is applied. Roentgenograms of 3 patients with excellent bony fusion were shown.

[ED. NOTE.—One of us has used this type of shoulder fusion in 2 cases with most satisfactory results. The posterior incision is simple; an adequate graft may be obtained from the scapula, and the position of the patient with the arm hanging down from the table simplifies the problem of maintaining the correct position during the operation.]

22. Dehne, E.: *Deutsche Ztschr. f. Chir.* **242**:40, 1934.

23. Scaglietti, O.: *Chir. d. org. di movimento* **18**:609, 1933.

*Operative Lengthening of the Femur.*—Putti<sup>24</sup> used skeletal traction with Kirchner wire to secure lengthening of the femur. One wire was inserted vertically through the great trochanter, the other through the femoral condyles. A simple oblique osteotomy was performed through the middle third of the femur. No mention was made of the division of soft parts. The leg was suspended on a Braun frame. The upper wire was fastened to the bed, and weight was gradually added to the lower wire beginning with 15 pounds (6.8 Kg.) and increasing by 1 or 2 pounds (0.5 or 1 Kg.) daily until the desired length had been obtained. This usually required from eighteen to twenty-one days, and the final weight was from 30 to 40 pounds (13 to 18 Kg.). The position was checked every third day by roentgenograms. When the desired length had been obtained the wires were incorporated in a snugly fitted plaster spica which was left on until fairly solid union had occurred. This usually required from eight to ten months. In 11 patients thus treated excellent results without complications were obtained.

*Reductions of Old and Irreducible Dislocations of the Shoulder Joint.*—From a large experience with dislocation of the humeral head Cubbins and his co-workers<sup>25</sup> concluded that there are a few fresh dislocations which cannot be safely reduced by closed manipulation with any of the usual maneuvers. For these and for old irreducible dislocations they devised a new operative approach designed to give adequate exposure of the glenoid. The patient is placed in the sitting position. The skin incision begins over the spine of the scapula, curves around by the lateral border of the acromion inward along the anterior border of the scapula to the anterior border of the deltoid muscle and then follows downward along the anterior border to the deltoid muscle. The clavicle and acromion origin of the deltoid muscle were divided, and the whole muscle is turned backward and downward. The capsule was opened longitudinally and the dislocation reduced. In two cases the long head of the biceps has been transplanted after the method of Nicola to prevent redislocation. The wound is closed by suturing the deltoid muscle back at its origin and closing the skin and subcutaneous tissues in the usual position. The arm is immobilized in the position of salute by a plaster cast for from four to six weeks.

#### FRACTURES

*Studies of 236 Compound Fractures.*—Daland<sup>26</sup> reported on 236 compound fractures observed at the Massachusetts General Hospital, including all types of fractures except those of the back and jaw.

24. Putti, V.: Surg., Gynec. & Obst. **58**:318, 1934.

25. Cubbins, W. R.; Callahan, J. J., and Suderi, C. S.: Surg., Gynec. & Obst. **58**:129, 1934.

26. Daland, E. M.: New England J. Med. **210**:983, 1934.

Daland concluded that if treated early and adequately, the average compound fracture caused by indirect trauma is no more serious than a simple fracture. If sepsis develops the period of disability is prolonged, and the end-result is not so good. The results obtained by cleansing the small puncture wound, applying an antiseptic solution and leaving the wound to granulate have been for the most part satisfactory. Compound fractures from direct trauma are far more serious and call for radical measures. Thorough débridement of a compound wound with adequate irrigation usually prevents the development of sepsis. Some of the smaller wounds may be tightly closed after débridement, but the larger ones should be left wide open. Loose or partial closure with drainage is not advocated. Carrel-Dakin therapy (as described by Daland <sup>26</sup>) correctly carried out was a satisfactory method for the treatment of infected or potentially infected wounds. Débridement prevented infection with gas bacilli, and gas bacillus serum was not needed as a prophylactic measure. Prophylactic antitetanic serum usually prevented tetanus or, if tetanus developed, lessened its severity. Bone ends should be débrided to prevent death of bone. Treatment by the described methods was satisfactory for all the bones with the exception of the femur and the bones of the leg. In these groups there was too much sepsis, and too few radical measures were resorted to.

*Compression Fractures of Vertebral Bodies.*—Bowler and Gile <sup>27</sup> based their report on 36 cases of compression fractures of the spine of which there were 7 with dislocation and involvement of the cord. Two of the patients died, one as a result of a pulmonary embolus and the other as a result of puncture of the hemiazygos vein and rupture of the liver. Laminectomy was not performed in any case. Bowler and Gile expressed the belief that traction would do as much for paraplegia as any other form of treatment. Hyperextension of the spine by means of the knee piece of a Gatch bed for from ten to fourteen days followed by the use of a plaster jacket for from ten to twelve weeks was the method of treatment suggested. A Taylor back brace was worn for the remainder of the year.

*Pathologic Fractures of the Spine Associated with Disorders of Calcium Metabolism.*—Moffatt <sup>28</sup> reported 4 cases of compression fractures of the spine due to calcium deficiency. He pointed out that lack of sufficient calcium is common in the average diet. Tumor of the pituitary or parathyroid glands may be the cause of disturbed calcium metabolism.

27. Bowler, J. P., and Gile, J. P.: *New England J. Med.* **210**:1052, 1934.

28. Moffatt, B. W.: *Pathologic Fractures of the Spine Associated with Disorders of Calcium Metabolism*, *Arch. Surg.* **28**:1095 (June) 1934.

*Fractures of the Patella.*—Cases of fracture of the patella constituted 1.22 per cent of the cases of fracture at the Massachusetts General Hospital as studied by Allen.<sup>29</sup> There was a total of 50 cases, in 38 of which studies of the end-results were made. Thirty-seven per cent of the 50 patients were operated on with sutures of kangaroo tendon, the fascia plaque method or the passage of a fascial strip through drill holes in the patella. The last method was preferred by Allen, and the technic of this procedure is described. It was felt that it gives more secure repair and permits earlier postoperative function of the joint. Studies of the end-results are reported.

*Epiphyseal Separation of the Long Bones.*—Eliason and Ferguson<sup>30</sup> reported 110 cases of epiphyseal separation of long bones; in 75 of these the end-results were based on at least a one year follow-up. Eliason and Ferguson found that the lower end of the radius was most frequently involved (48 cases); the lower part of the humerus including the epicondyles was involved in 36 cases; the lower part of the ulna, in 9, and the lower part of the tibia, in 4. The other epiphyses were involved not oftener than 3 times each in this series. There were 2 cases of separation of the head of the femur, but it is noted that they were not purely traumatic in origin. In 85.3 per cent of the cases excellent or good anatomic and functional results were obtained. In only 3 cases did premature ossification occur. This happened in spite of perfect early anatomic reduction. Other cases in which fair or poor anatomic reductions took place did not show premature ossification, and growth appeared to continue normally. The chief danger of imperfectly reduced epiphyseal separation is limitation of motion in the joint. No study of age groups was made.

*Inadequate Immobilization and Nonunion of Fractures.*—While conceding that many pathologic and biochemical factors may be concerned in the rate of union of fractures, Jones<sup>31</sup> stated that the only one which is of practical importance in determining nonunion is inadequate immobilization. Adequate immobilization implies that no movement is possible within the splints or plasters and that this state is maintained for a sufficient length of time. The duration of the necessary immobility varies with individual fractures. Nonunion of the first stage, i. e., before sclerosis supervened, was cured by immobilization, but nonunion of the second stage required drilling or grafting. In infected compound fractures the transition from the first to the second stage was marked by quiescence of the infection.

29. Allen, A. W.: J. Bone & Joint Surg. 16:640, 1934.

30. Eliason, E. L., and Ferguson, L. K.: Surg., Gynec. & Obst. 58:85, 1934.

31. Jones, R. W.: Brit. M. J. 1:936, 1934.

## RESEARCH

*Growth of Connective and Osseous Tissue in the Presence of Certain Minerals.*—Menegaux and his co-workers<sup>32</sup> carried out more than 1,000 experiments in which they tested the effect of various metals on the growth of connective and osseous tissue (osteoblasts) in vitro. Mediums were used in which cells grew and multiplied rapidly. Bits of the metal to be tested were then introduced into the culture; the effect on all growth was observed and the results compared with those in control cultures in which no metal had been placed. The conclusions were as follows: 1. Copper, magnesium, iron, soft steel and aluminum bronze showed a toxicity which completely inhibited cellular growth. It was thought that possibly the use of soft steel and aluminum bronze accounted for some of the tissue necroses and bone absorption frequently observed.

2. Zinc, silver, tungsten, nickel and tin and aluminum alloys were less toxic but nevertheless inhibited all growth sufficiently to indicate that probably these metals should not be used in the human body.

3. Gold, aluminum and lead were entirely nontoxic. Unfortunately the physical properties precluded their use in surgical procedures. Duraluminum, which has the physical characteristics of soft steel, and the rustless steels designated as "V. A. Extra" "Nickel O" and "Platim-stainless" also proved to be nontoxic and were considered the best to use in surgical procedure and osseous repair.

*Contribution to the Study of Bone Transplants.*—Comitz and his co-workers<sup>33</sup> transplanted carefully fitting pieces of bone with periosteum from the right to the left tibia and vice versa in 17 dogs. The grafts were studied at intervals varying from forty-eight hours to one hundred and ninety-six days. Beginning union of the transplanted bone was observed in seventy-one hours, and the process was not complete in one hundred and ninety-six days. In five days proliferating connective tissue was seen about the graft. This changed rapidly to a callus of connective tissue. This process was observed in the superficial osseous tissue and in the endosteum. The callus slowly adopted the character of bone callus. In forty-two days the callus formed from myelogenous tissues had almost completely disappeared. The periosteal callus was still present after sixty days, but advanced degeneration was observed in it. In the peripheral part of the graft lamellated bone formation was observed simultaneously with the breaking down of the callus. Certain parts of the graft were remolded; other parts retained their original structure. The authors looked on periosteal and mye-

32. Menegaux, G.; Moyse, P., and Odiette, D.: Presse méd. 42:658, 1934.

33. Comitz, H.; Holmgren, H., and Johansson, H.: Acta chir. Scandinav. 75:1, 1934.

ogenous callus as an expression of disturbances in the mechanics and dynamics of bone. In young animals the callus at times showed cartilage formation. Osteoclasts were seen after seven days and persisted in all observations after that period. They were the end-stage of osseous protoplasm stripped of calcium and collagen fibers. No prominent part was played by the periosteum or endosteum of the graft, but the periosteum and endosteum of the host were important in the formation of the first fibrous callus.

*Influence of Venous Stasis on Heterotopic Formation of Bone.*—Roome and McMaster<sup>34</sup> observed the action of venous stasis on the heterotopic formation of bone. In 6 dogs epithelium from the bladder was sutured to the muscles of the leg on both sides. On one side the femoral vein and its chief tributary branches were ligated. The animals were observed roentgenologically and later killed. Denser bone formation was observed on the side where the veins had been ligated.

*Influence of Bladder Transplants on the Healing of Defects in Bone.*—Copher and Key<sup>35</sup> studied the effect of transplants of bladder epithelium on the healing of defects in bones. Basing their study on the finding of Huggins<sup>36</sup> that bladder epithelium produced bone when transplanted to other portions of the body, they transplanted epithelium from the bladder to a 1 cm. bone defect in the ulna in 24 dogs. A 1 cm. defect was found in previous experiments to lead to nonunion in almost every case. A similar 1 cm. defect was made in the ulna of the opposite side to serve as a control. Definite stimulation of osteogenesis was observed in the bladder transplant with later bridging of the gap and absence of atrophy on the ends of the bone.

*Experimental Muscular Atrophy.*—Thompson<sup>37</sup> immobilized the hindlegs of rabbits in plaster of paris, some in a weight-bearing position and others in a nonweight-bearing position. The changes produced in the muscle were much more striking in the latter than in the former position. After a few days there was edema, and the muscles were flabby, moist and pale. After from six to eight weeks the muscles were no longer distinct, elastic, compact groups but were soft masses of pale, edematous material with areolar and fibrous tissue scattered through them.

34. Roome, N. W., and McMaster, P. E.: Influence of Venous Stasis on Heterotopic Formation of Bone, Arch. Surg. 29:54 (July) 1934.

35. Copher, G. H., and Key, J. A.: Influence of Bladder Transplants on the Healing of Defects of Bone, Arch. Surg. 29:64 (July) 1934.

36. Huggins, C. B.: The Formation of Bone Under the Influence of Epithelium of the Urinary Tract, Arch. Surg. 22:377 (March) 1931.

37. Thompson, T. C.: J. Bone & Joint Surg. 16:564, 1934.

*Effects of Tuberculo-protein on the Course of Experimental Tuberculosis in Rabbits and Guinea-Pigs.*—According to Smithburn and his co-workers,<sup>38</sup> rabbits and guinea-pigs subjected to a long series of daily injections of tuberculo-protein became hypersensitive to this substance, as indicated by the intracutaneous reaction. Accompanying this induced hypersensitiveness there was an abolition of the temperature response induced by the protein. Little or no effect on resistance to tuberculosis in either rabbits or guinea-pigs was produced by the tuberculo-protein. This work adds to the growing evidence that allergy and immunity to tuberculosis may be largely unrelated phenomena.

---

38. Smithburn, K. C.; Sabin, F. R., and Geiger, J. T.: *Am. Rev. Tuberc.* **29**: 562, 1934.

# ARCHIVES OF SURGERY

VOLUME 30

MAY 1935

NUMBER 5

## CANCER OF THE CHEEK (BUCCAL MUCOSA)

STUDY OF NINETY-NINE CASES WITH RESULTS OF  
TREATMENT AT THE END OF FIVE YEARS

HAYES E. MARTIN, M.D.

Attending Surgeon, Memorial Hospital

NEW YORK

AND

OTTO H. PFLUEGER, M.D.

Formerly Resident Surgeon, Memorial Hospital

SAN FRANCISCO

During the five year period from 1925 to 1929, ninety-nine cases of carcinoma of the cheek the records of which are sufficiently complete to form a basis for this clinical study were observed in the clinic at Memorial Hospital. This series includes all of the cases of cancer of the cheek, in both the early and the hopelessly advanced stage, in which we had histologic proof of the presence of cancer, and in which there was subsequent observation for at least one month or until death. We excluded those cases in which the disease was not proved histologically, for instance, those in which, although the condition clinically appeared to be cancer, papilloma only was revealed on histologic examination. We also excluded the cases of those patients ("clinic shoppers") who made but one or two visits to the clinic and were then lost track of within one month, without receiving the proffered treatment. The reported end-results are based on the histories of patients observed for five years or longer. Since we have included the cases of hopelessly advanced disease (thirty-two, or 32 per cent) in which palliative treatment only was given, we offer this report as an index of the disease as it is seen at the time when the patients first apply for treatment. Twenty-four patients (24 per cent) had received unsuccessful treatment by surgical excision, cautery or irradiation previous to their application at the clinic. In the case of nine of these, local surgical excision of the primary lesion had been made.

### ETIOLOGY

Carcinoma of the cheek (buccal mucosa) comprises 9.5 per cent of all of the intra-oral tumors (Pack and Le Fevre<sup>1</sup>). In this group of

Read at a meeting of the American Radium Society, Cleveland, June 1934.

1. Pack, G. T., and Le Fevre, R. G.: *The Age and Sex Distribution and Incidence of Neoplastic Diseases at the Memorial Hospital, New York City, J. Cancer Research* 14:167, 1930.



neoplasms, it ranks third in frequency, cancer of the tongue (20.6 per cent) and cancer of the lip (15.4 per cent) being the most common forms. It is chiefly a disease of old age and is seen less often in young people than is any other form of intra-oral cancer. The average age of the patients in our series was 59. The oldest patient was 97 and the youngest 33. About 50 per cent of the cases occurred in the fifth and sixth decades of life. The disease is over nine times as frequent among men as among women. Nine cases only, or 10 per cent, in our series occurred in women.

The right and the left cheek were involved in almost the same number of instances; it seems that findings such as those of Steiner,<sup>2</sup> who reported that in 70 per cent of thirty-three cases the disease was noted on the left side, are purely accidental. The midportion of the cheek, opposite the occlusal level of the teeth, is the site most often involved (40 per cent), although the disease may appear at any point on the buccal mucosa or in either of the buccogingival grooves. A considerable number of carcinomas arise just posterior to the labial commissure. Direct local extension of the primary growth into the adjacent soft parts may take place early in the course of the disease. Local extension of this kind was found at the time of admission to the clinic, in over 60 per cent of our cases.

Chronic irritation is a more obvious etiologic factor in carcinoma of the cheek than in any other type of intra-oral cancer. The most common chronic irritants to the buccal mucosa are sharp or broken teeth, ill-fitting dental appliances, syphilis and tobacco. The last agent acts both by the production of local heat and by chemical irritation. Davis<sup>3</sup> attributed the prevalence of carcinoma of the cheek in the Philippine Islands to the chewing of buyo, which is a combination of buyo leaf, betel nut, slaked lime and tobacco—a habit most common among the Philippine women. It is interesting to note that Davis reported the incidence of cancer of the cheek as greater among women than among men. We found definite evidence of dental irritation in twenty-three cases (23 per cent), either from sharp teeth or from ill-fitting dentures.

Leukoplakia is a common precancerous response of the mucous membranes composed of flat pavement epithelium to chronic irritations. Intra-oral leukoplakia occurs most often in the mucosa of the cheek; it was specifically noted in 22 per cent of the accompanying cases. In a special investigation of the incidence of leukoplakia among the cases of intra-oral cancer in our clinic, the condition was found in about 70 per cent of the cancers of the cheek. Carcinoma may arise in a patch of

2. Steiner, P.: Beiträge zur Krebsstatistik, *Deutsche Ztschr. f. Chir.* **24**: 363, 1906.

3. Davis, G. G.: Buyo Cheek Cancer, *J. A. M. A.* **64**:711 (Feb. 27) 1915.

leukoplakia or in apparently normal mucous membrane adjacent to a patch of leukoplakia. In susceptible persons chronic irritation may produce either cancer or leukoplakia or both, and in certain instances the leukoplakia may undergo malignant change. We have observed cases of generalized intra-oral leukoplakia for from ten to twelve years without noting a malignant change.

As a chronic irritant, syphilis, in the form of syphilitic glossitis, is a predisposing factor in all of the anatomic varieties of cancer of the oral cavity proper. Wassermann tests, made in thirty-eight of our cases, gave positive results in six, or 15 per cent.

#### DIFFERENTIAL DIAGNOSIS

The differential diagnosis is not ordinarily difficult. In all of the cases in which cancer of the oral cavity is suspected, a biopsy should be made at the time of the first examination in order to verify the clinical diagnosis.

The diseases other than cancer which most commonly present ulcerated lesions of the buccal mucosa are syphilis, tuberculosis, superficially ulcerated or fissured leukoplakia, herpes and simple granulomas (trauma, Vincent's angina and so on).

Syphilitic lesions may exactly simulate cancer in their clinical appearance. A correct diagnosis is obtained only if repeated biopsies fail to reveal the presence of cancer, if the Wassermann reaction is positive and if the lesion disappears after two or three weeks of intensive anti-syphilitic treatment. A positive Wassermann reaction alone does not disprove the presence of cancer. The two diseases coexist in a large percentage of cases.

Tuberculous ulcers may occur on the buccal mucosa, but they are more common on the tongue. Such ulcers usually present a yellowish, unhealthy base, as compared to the coarse, granular appearance of cancerous lesions; they are more likely to be tender and painful. The diagnosis is made by the aid of biopsy (preferably repeated) which fails to show the presence of cancer, roentgen examination of the chest and examination of the sputum. Tuberculous ulcers of the oral mucous membranes are almost invariably secondary to demonstrable pulmonary tuberculosis.

Long-standing leukoplakia of the cheek may present superficially ulcerated or fissured areas which are prone to undergo malignant change. Tissues for biopsy should always be taken from such suspected areas. Local treatment by irradiation or by cautery should be given in all of these cases, despite failure of biopsy to reveal cancerous tissue.

A definite diagnosis of simple granuloma should never be made without repeatedly negative results of biopsy. The biopsy may be withheld temporarily if there is a history of recent adequate trauma, such

as the biting of the cheek, or if a painful, tender ulcer, such as those present in herpes or in Vincent's disease, suddenly appears. If such an ulcer persists longer than two weeks, a biopsy is definitely indicated.

#### PATHOLOGIC LESIONS

By histologic examination, cancer of the cheek is found to be epidermoid carcinoma in 95 per cent of the cases. Adenoid tumors may arise from minor salivary glands of the buccal mucosa. One case of myxosarcoma occurred in the present series. In table 1 the distribution of the histologic types of carcinoma of the cheek among the successfully

TABLE 1.—*Distribution of Ninety-Nine Cases of Cancer of the Cheek on the Basis of the Histopathologic Type and Malignancy of the Neoplasm and the Number and Percentage of Cures*

Type of Cancer	Number of Cases	Cures at End of Five Years
Epidermoid carcinoma, grade I.....	38	15 (39%)
Epidermoid carcinoma, grade II.....	53	11 (20%)
Epidermoid carcinoma, grade III.....	3	0
Adenocarcinoma.....	4	2
Myxosarcoma.....	1	0
Total number of cases of all types.....	99	28

and the unsuccessfully treated groups is recorded, and the prognostic significance of tumor grading is indicated. It is to be noted that 39 per cent of grade I tumors were controlled for five years or longer, but that only 20 per cent of grade II tumors so responded.

#### SYMPTOMS

In common with all types of cancer, carcinoma of the cheek is essentially symptomless in its early stages. It first appears as a small, ulcerated, indurated mass, which may or may not protrude above the surface of the mucosa. Unless the lesion begins in the center of the cheek, the tendency is toward an early invasion of the upper or the lower jaw, the lateral pharyngeal wall or the palate. It seems that, with the assistance of the acute tactile sense of the tongue, the presence of a roughened area or ulcer on the sensitive mucosa of the cheek should be easily noted, but such signs are at first almost always disregarded, and the patient thinks that he has unconsciously bitten his cheek or that he has a "canker sore." By one who is careless of oral hygienic care, the irritation of a sharp tooth is as complacently disregarded and neglected as are the decay and loss of the teeth themselves. In only about 8 per cent of the cases in our series was the primary lesion, at the time of admission, less than 2 cm. in diameter, and in about 30 per cent it was between 3 and 4 cm. About one third of the patients reported "sore-

ness" as the first symptom, which indicates that no particular attention was paid to the presence of the lesion until it was far advanced and deep fissuring infection or even sloughing had occurred. The other two thirds of the patients complained of no symptom but the presence of the lesion.

The average duration of the symptoms, according to the statements of the patients, was nine months, and in only eighteen cases (18 per cent) did the history of symptoms cover less than two months. In two cases, the patient had sought medical advice because of enlarged cervical nodes. In one of these cases a biopsy had been made on material from a cervical node, after which the patient was referred to the Memorial Hospital with the diagnosis of "squamous carcinoma of the neck." The mouth was in a fetid condition, owing to a massive, fungating, necrotic tumor of the cheek, which the patient had apparently not considered worthy of mention.

TABLE 2.—*Local Extension of Carcinoma of the Cheek at the Time of Admission in a Series of Ninety-Nine Cases*

Location of Extension	Number of Cases
Upper jaw alone.....	7
Lower jaw alone.....	15
Both upper and lower jaws.....	5
Mucosa over ascending ramus of mandible.....	11
Upper jaw and mucosa over ascending ramus of mandible.....	4
Lips .....	13
Total number of extensions.....	61

Direct extension of the primary lesion into the adjacent soft parts is common and may occur early in the course of the disease. In sixty-one (61 per cent) of the cases at the time of admission extension had taken place beyond the mucosa of the cheek, as indicated in table 2.

This early tendency toward the invasion of the neighboring structures suggests at once the unsuitability of the disease to surgical measures for the control of the primary lesion and it explains the indifferent surgical results reported in the literature. Extension to the lower jaw alone or to the lips might be dealt with by extensive surgical procedures, but the involvement of the lateral pharyngeal wall or of the palate offers little chance of control, even by the most extensive surgical intervention.

As the tumor enlarges, it becomes fissured and necrotic from the trauma involved in stretching the cheek and in biting during mastication. Infection takes place, followed by swelling of the cheek and tenderness or pain. As the cheek becomes infiltrated by the growth and as infection develops, its elasticity is lost, and mastication and the opening of the mouth are interfered with. If the growth is located posteriorly, so that

the infiltration and the infection occur in the neighborhood of the pterygoid and temporal muscle and their tendons, trismus ensues. The tumor may fungate into the mouth and form an oozing, sloughing, fetid mass, or it may perforate the cheek and appear externally on the surface of the skin. Extension may occur, either early or late, to the upper or the lower jaw, backward into the pharynx or anteriorly into the angle of the mouth or into the upper or the lower lip. Unless the disease invades the upper or the lower jaw, through sockets of teeth, invasion of the bone is apt to be a late manifestation, for the normal periosteum is resistant to the local extension of a carcinoma. In the untreated patient, the tumor usually tends to perforate the skin of the cheek and extend directly to the upper and the lower jaw.

Eventually, local infection, pain and trismus appear. Metastasis to the submaxillary lymph nodes with mixed infection complicates the clinical course. Hemorrhage from erosion of the internal maxillary or facial artery may take place. Death ensues from a combination of causes: infection, pain, malnutrition and hemorrhage. As is the case in most forms of intra-oral cancer, the disease usually causes death without progressing below the clavicle.

#### METASTASES

Metastases tend to occur comparatively late in the course of the disease. In this series, despite the fact that the average duration of symptoms prior to admission was nine months, fifty-six patients (56 per cent) had no palpable nodes at the time of admission. In at least fifty-one (51 per cent) but in not more than fifty-six, metastases developed at some time during the course of the disease, and in all but eleven of these the submaxillary lymph nodes only were involved. In all but one of the patients with metastases occurring beyond the submaxillary triangle, the primary lesion was posteriorly located and had extended backward into the tonsillar region, and the metastases had occurred to the upper deep cervical nodes.

With the exception of the eleven cases just mentioned and of one to be noted later, the disease did not extend beyond the submaxillary triangle, and it was controlled or the growth was limited to the cheek, the contiguous structures and the submaxillary triangle at the time of death. In two cases, there was metastasis bilaterally to the submaxillary triangle; in each of these instances extension, anteriorly, had taken place across the midline into the upper lip. In one case of bilateral metastasis, death was due to metastasis to the liver (observed at autopsy); in another, in which the primary lesion was situated posteriorly, widespread metastases occurred to the skin of the thoracic wall, following a radical dissection for the involvement of the submaxillary and the upper deep

cervical lymph nodes. In these two cases appeared the only extensions below the clavicle. As a general rule, the disease does not extend beyond the submaxillary triangle, an observation of great importance in dealing with metastases to the nodes of the neck. Its significance is further discussed in connection with the treatment.

## TREATMENT

We are of the opinion that the most successful treatment of carcinoma of the cheek is by a combination of irradiation and surgical intervention. From the published results, it appears that surgical treatment alone is far less successful in this disease than in cancer of the lip and of the tongue. We shall subsequently discuss the surgical aspects at greater length.

TABLE 3.—*Occurrence and Treatment of Metastases in Ninety-Nine Cases of Cancer of the Cheek*

Patients with metastases:	Number
Present at time of admission.....	43
Appearing after time of admission.....	5
Total .....	48 (51%)
Of possible later occurrence in patients who died of the disease but were not continuously observed.....	5
To submaxillary triangle only.....	40
To submaxillary triangle, upper deep cervical nodes or beyond.....	11
Bilaterally to submaxillary triangle.....	2
Below clavicle .....	2
Metastases present at some time during course of disease in twenty-eight successfully treated patients.....	9 (32%)
Treated by irradiation and neck dissection.....	6
Treated by irradiation alone (external irradiation and by implants of radon) .....	3

At the outset, one should decide whether the treatment is to be an attempt at cure or to be merely palliative. In the case of far advanced disease, any attempt at cure usually increases the suffering and shortens life. If treatment by irradiation is instituted, the quantity of radon in the implants necessary to produce complete regression is practically in direct proportion to the volume of the neoplastic mass, and the surgeon must first decide whether a curative dose of this size will be reasonably well tolerated by the patient.

In the treatment of cancer of the cheek, three distinct problems must be considered: the hygienic care of the oral cavity before and during the treatment, the treatment of the primary lesion and the management of the cervical metastases.

*General Hygienic Measures.*—In most instances, the hygienic condition of the oral cavity is poor, and this complication is always increased temporarily during the treatment by irradiation. Decayed or sharp teeth, coated with epithelial debris, are almost always present.

Before instituting treatment, prompt measures must be taken to improve the oral hygiene. A sharp tooth, especially if in contact with the lesion, should be filed smooth or possibly extracted, but the wholesale extraction of teeth should be avoided, as the attendant laceration of the gums temporarily increases oral sepsis and delays treatment. The extraction of teeth following heavy irradiation is so commonly followed by osteomyelitis that in spite of the chances of the local spread of the disease we often advise the extraction of a limited number of condemned teeth.

In all of the cases, the surfaces of the teeth should be thoroughly cleaned by a dentist, and the patient instructed in the use of a toothbrush, with which he is apt to be unfamiliar. As a mouth wash, compound solution of sodium perborate, should be used, and copious irrigations with saline solution are of great value until the reaction from irradiation has subsided. We usually insist on daily visits to the clinic during the first few weeks of treatment, at which times the oral cavity and the interstices between the teeth are cleansed with a power spray of surgical solution of chlorinated soda, U. S. P. A vigorous combating of the oral sepsis is of great value in conserving the general strength and the nutrition during what may be a trying period.

*Treatment of the Primary Lesion.*—The primary lesion should be treated almost entirely by irradiation. In the series here reported on, the plan was first to give one application of external irradiation. In most cases, roentgen radiation (200 kilovolts and a filter of 0.5 mm. of copper and 1 mm. of aluminum) was given to the affected side in a dosage of from 600 to 700 r units (roentgens) at a distance of 50 cm. The skin portal included the primary lesion and the submaxillary triangle. In a few cases, the radium element pack was used to deliver about the same skin dose at a distance of 6 cm. This dosage was ordinarily a little more than 1 skin erythema dose; by this means, a diffuse depth dose was delivered both to the primary lesion and to any possible metastasis. Following this, a tray with an area of 20 sq. cm., and a filter of 2 mm. of brass, at a distance of 3 cm., was applied externally to the cheek opposite the primary lesion, and a dose of from about 2,500 to 3,000 millicurie hours given. This application was directed chiefly locally to the base of the primary lesion, as it were, attacking it from beneath. These two procedures by the use of external irradiation are almost always applicable, and were employed more or less as a routine in our technic. At the present time, we give the external radiation through the cheek to the primary lesion in multiple divided doses, but since this technic was not used in the series reported here, it is not described in detail at this point.

Following external irradiation, interstitial irradiation was employed in the form of gold implants (with a filter of 0.3 mm. of gold), which

were inserted into the primary lesion. With this method we prefer implants, rather than needles, owing to the difficulty, or often the impossibility, of maintaining the latter in position in a thin or a fragile mass. After a careful measurement of the primary lesion with calipers, an applicator dose of gold seeds is prescribed, which delivers from 7 to 10 skin erythema doses to the neoplastic mass (table 4). In this measurement, the mass is considered as a sphere the diameter of which is equal to the longest diameter of the primary lesion. In growths of very irregular shape, two or more adjacent or overlapping spheres may be considered, and the dose for each calculated separately. A more detailed discussion of this method for the calculation of the dosage has been published by one of us (Dr. Martin<sup>4</sup>). The number of millicuries of radon in the gold implants necessary to produce the specific

TABLE 4.—*Millicuries of Radon in Gold Seeds Required to Deliver Specified Skin Erythema Doses to Tumors of Various Diameters*

Skin Erythema Doses	Diameter of Mass, Cm.											
	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	6.0	7.0	8.0
	Millicuries of Radon											
1.....	0.2	0.5	0.8	1.5	2.0	2.4	2.9	3.4	4.0	5.4	7	9
2.....	0.4	1.0	1.6	3.0	4.0	4.8	5.8	6.9	8.0	11	14	18
3.....	0.6	1.5	2.4	4.5	6.0	7.2	8.7	10	12	16	21	27
4.....	0.8	2.0	3.2	6.0	8.0	9.6	12	14	16	22	28	36
5.....	1.0	2.5	4.0	7.5	10	12	14	17	20	27	35	45
6.....	1.2	3.0	4.8	9.0	12	14	17	20	24	32	42	54
7.....	1.4	3.5	5.6	10	14	17	20	24	28	38	49	61
8.....	1.6	4.0	6.4	12	16	19	23	27	32	43	56	72
9.....	1.8	4.5	7.2	14	18	22	26	31	36	49	63	81
10.....	2.0	5.0	8.0	15	20	24	29	34	40	54	70	90
11.....	2.2	5.5	8.8	17	22	26	32	37	44	59	77	100
12.....	2.4	6.0	9.6	18	24	29	35	41	48	65	84	108
13.....	2.6	6.5	10	20	26	31	38	44	52	70	91	117
14.....	2.8	7.0	12	21	28	34	41	48	56	76	98	126
15.....	3.0	7.5	13	23	30	36	44	51	60	81	105	135

tissue doses in masses of various diameters are given in table 4. All of the irradiation should be completed in from seven to fourteen days.

The technic just described is designed for the primary lesion as usually seen, and in these cases, except for the hygienic care already mentioned, no further therapeutic measures are taken.

In this series, the largest dose of radon gold seeds given to a successfully treated patient was 20 millicuries. The doses most frequently used with success ranged between 8 and 16 millicuries (figs. 1 and 2).

In certain instances, often not in the most malignant cases, the growth tends to fungate into the mouth rather than to infiltrate the cheek deeply. In such cases, the period of convalescence is shortened by removing the tumor mass to the level of the mucosa by actual cautery

4. Martin, H. E., and Quimby, E. H.: Calculations of Tissue Dosage in Radiation Therapy, *Am. J. Roentgenol.* **23**:173, 1930.



about a week or ten days following the interstitial irradiation. By this procedure, the implants are removed before they have delivered their total energy; their initial quantity, therefore, should be correspondingly greater.

As already mentioned, at the present time we are giving the external irradiation through the cheek to the primary lesion in multiple divided doses of roentgen radiation, rather than by the use of the single dose of roentgen rays and the radon tray. About 2,500 to 3,500 r units are given in from ten to fifteen divided doses over a period of from two to three weeks, with a circular skin portal 7 or 8 cm. in diameter. We are of the opinion that this technic is of great value, since the primary



Fig. 1.—*A*, squamous carcinoma of the cheek, grade I, diagnosed at biopsy. Treatment was administered by a radon tray, with an exposure of 3,000 millicurie hours at a distance of 3 cm., and by the implantation of 15 radon gold seeds of 20 millicuries in the primary lesion; *B*, complete healing of the lesion with no recurrence of the disease after five years.

lesion often diminishes markedly in size and requires a lesser dose of radon seeds than would otherwise be required. The decision as to when the external irradiation should be discontinued and the seeds implanted must be guided by clinical experience, but the implantation should follow almost immediately the external irradiation. We have in a few instances obtained complete regression of the primary lesion in the cheek by divided doses of roentgen radiation alone; usually, however, the growth is too resistant to the roentgen rays for successful control by that method alone, and in most cases we advise against the attempt.

*Treatment of Metastases.*—This problem should be considered separately. If no nodes are palpable at the time of admission, we usually give one treatment by external irradiation to the cervical region, following which no further treatment is given to the neck until definite palpable evidence of the presence of metastases appears.

We are opposed to prophylactic neck dissection.<sup>4a</sup> The validity of this view is evident from the statistical data obtained in this study. In at least 44 per cent of the cases metastases developed at no time during the course of the disease, and in fifteen

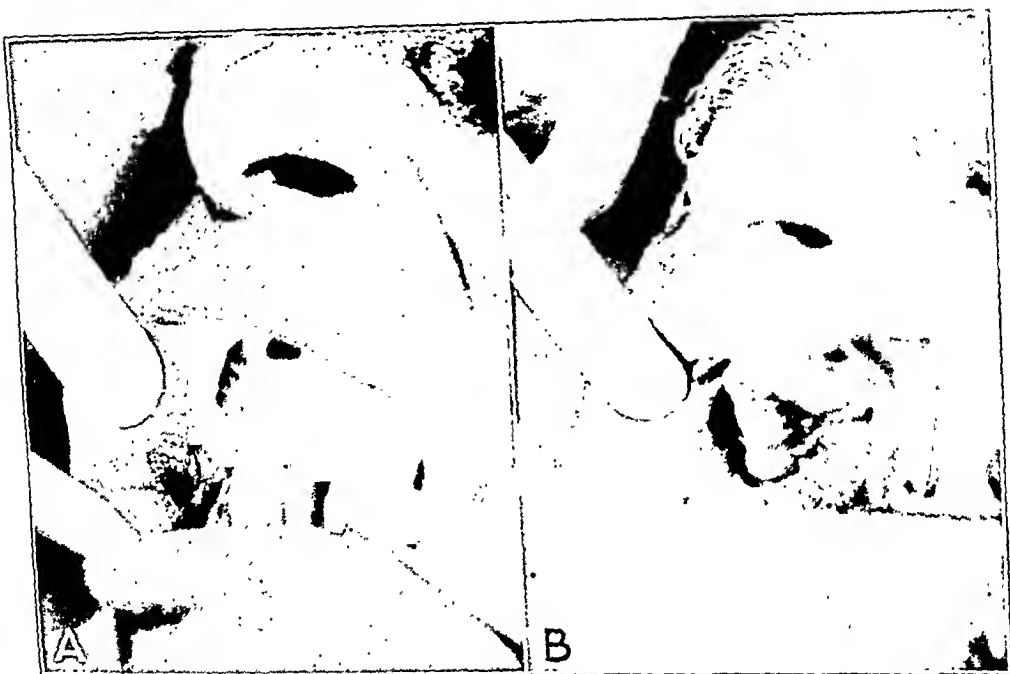


Fig. 2.—A, squamous carcinoma of the cheek, grade II, diagnosed at biopsy. Treatment was administered by a radon tray, with an exposure of 3,000 millicurie hours at a distance of 3 cm., and by the implantation of radon gold seeds of 5 millicuries into the primary lesion; B, complete healing of the lesion with no recurrence after five years.

cases death is known to have occurred from local extension of the disease, but without metastases. Of the twenty-eight successfully

4a. By neck dissection we mean the removal of all lymph node-bearing tissue between the skin and the deep muscle fascia of the neck from the lower edge of the mandible to the clavicle and from the anterior border of the trapezius to the midline of the neck, including the submaxillary salivary gland, the sternocleidomastoid muscle, the superficial veins and the jugular vein. By submaxillary dissection we mean the removal of all lymph node-bearing tissue between the skin and the deep muscle planes of the submaxillary triangle, including the submaxillary salivary gland.

treated patients, twenty-four (85 per cent) were without palpable nodes at the time of admission. Of the twenty-four, five (20 per cent) presented metastases within from three months to one year. In no case did metastases develop later than one year following the control of the primary lesion. Of the fifty-six patients presenting no metastases at the time of admission, among whom are included both those successfully and those unsuccessfully treated, in only eight, or 14 per cent, did metastatic nodes of the neck appear later. Routine prophylactic neck dissection would therefore have necessitated fifty-six operations in order that possible benefit might result in eight cases. It appears that no further proof is required to demonstrate the lack of justification for the employment of prophylactic neck dissection in cases of cancer of the cheek.

If metastases are present at the time of admission, our usual procedure is either to perform a neck dissection after the control of the primary lesion or to insert gold seeds after the surgical exposure of the nodes by a short incision through the skin and superficial tissues only. This exposure permits a more accurate measurement of the node, which is essential in the determination of the dosage and, furthermore, permits an accurate placement of the implants. Quick<sup>5</sup> has published the technic which we employ in the combined surgical and radiologic method of treatment of metastatic nodes of the neck. Neck dissection or any extensive surgical procedure is to be avoided, if possible, during the aggressive irradiation of the primary lesion. If metastases appear for the first time, or additional nodes become palpable after the subsidence of the reaction from radiation in the cheek, we have, in the past, performed a submaxillary dissection on the affected side. In this series, we performed dissections of the cervical nodes in twenty-three cases. In six of these, there was no recurrence, either in the cheek or in the neck. In twenty-eight cases the metastases were treated by irradiation alone in the form of external irradiation and radon seeds inserted either through the skin or after limited surgical exposure. In seven of these complete regression without recurrence took place, although four patients died of local extension of the primary lesion. Since the specific form of therapy for the surgically treated and irradiated groups of metastases was chosen to suit the particular case, we do not think that the statistics just cited necessarily present a fair picture of the relative merits of surgical treatment and irradiation. The cases chosen for neck dissection were those in which the primary lesion was under control and in which cervical nodes were freely movable and oper-

---

5. Quick, D.: Interstitial Radiation in Metastatic Cervical Nodes of Epidermoid Carcinoma, *Ann. Surg.* **93**:380, 1931.

able. The metastases which were treated by irradiation only in most cases were fixed and inoperable or occurred in those patients in whom the primary lesion was extensive. In the patients treated palliatively, all of the metastases were given irradiation only. Of late, we have tended to depend more on the use of interstitial implants in the treatment of enlarged nodes of the neck.

It should be realized that in many of the moderately advanced cases, in which the average age is about 60, the general condition of the patient may necessitate wide variations in management. Invasion of the mandible by the primary lesion or the attachment of metastases to the bone may require resection of a portion of the mandible. This was done in two of the cases. If a submaxillary node has not perforated its capsule but has become definitely attached to the mandible, it may often be removed with the attached bone by the excision of the crescent-shaped portion of the mandible only. Severing of the continuity of the mandibular arch is thereby avoided.

#### COMPLICATIONS

In case of hemorrhage from erosion of the facial artery by an extensive uncontrolled primary lesion, ligation of the external carotid artery may be necessary.

Local necrosis of the soft tissues of the cheek sometimes follows heavy irradiation. It seldom extends through the entire thickness of the cheek, and if the growth has been controlled it does not seriously alter the end-result, although it may delay healing. Local necrosis in this series was not definitely associated with the use of large doses of radon implants, and we are of the opinion that the most common causes of local breaking down of the tissues are the poor distribution of the implants and the unnecessary introduction of infection during the procedure of implantation. In certain cases, local necrosis of the cheek followed the neck dissection, during which the facial artery is always severed.

Osteomyelitis of the mandible may follow the heavy irradiation of extensive disease in the lower gingivobuccal gutter or its extension to the lower jaw. If osteomyelitis does not involve the entire cross-section of the mandible, conservative treatment is indicated, awaiting the separation of the sequestrum. If osteomyelitis has involved the entire cross-section of the lower jaw, resection of a portion of the mandible may be indicated. The operation is performed through the mouth without skin incisions; external scarring and injury to the facial nerve are thereby avoided. The procedure is followed by less deformity than might be expected if the anterior portion of the mandibular arch and the anterior attachments of the two digastric muscles can be spared.

In resecting a portion of the horizontal ramus, we remove as well the ascending ramus, which, if left by itself, is a mechanical nuisance and delays healing. We have considered that operations of bone grafting were seldom applicable within the five year period following the treatment of such a lethal disease as cancer of the cheek.

#### PROGNOSIS AND RESULTS OF TREATMENT

Morestin <sup>6</sup> stated that carcinoma of the cheek has the worst prognosis of any of the intra-oral cancers, whereas New <sup>7</sup> and Brewer <sup>8</sup> have even declared that its malignancy is exceeded only by that of melanoma. With these opinions we cannot agree. Polya <sup>9</sup> expressed the opinion that cancer of the cheek is more malignant than that of the lip but less malignant than that of the tongue. Under proper treatment, the prognosis of carcinoma of the cheek should be about the same as that of cancer of the lip, were it not for the fact that cancer of the lip is usually discovered earlier in the course of the disease, with a consequent lessened chance of metastases and with the primary lesion more amenable either to irradiation or to surgical treatment. This advantage is somewhat counterbalanced by the tendency of metastases from cancer of the lip to advance bilaterally or beyond the submaxillary triangle. Carcinoma of the cheek metastasized beyond the submaxillary triangle in only about 10 per cent of our cases, but the primary lesion is usually more advanced and is not so accessible either to surgical measures or to irradiation. Histologically, cancer of the cheek and that of the lip are similar.

As compared to cancer of the lip and of the tongue, there are relatively few strictly surgical observations and statistics on cancer of the cheek in the literature. The few surgical statistics which have been published are incomplete and unsatisfactory as to the period of observation and the method of the selection of cases. From surgical treatment alone the only results at the end of five years which we have been able to find reported are those of Simmons,<sup>10</sup> who, from a selected group of thirteen patients in all of whom there were no metastases at the time of admission, reported six patients (48 per cent)

6. Morestin, H.: Cancer de la joue, *Rev. gén. de clin. et de thérap.* **14**: 516, 1900.

7. New, G. B.: The Use of Heat and Radium in the Treatment of Cancer of the Jaws and Cheek, *J. A. M. A.* **71**:1369 (Oct. 26) 1918.

8. Brewer, G. E.: Carcinoma of the Lip and Cheek, *Surg., Gynec. & Obst.* **36**:169, 1923.

9. Polya, E.: Technique of Operations for Carcinoma of the Buccal Mucous Membrane, *Surg., Gynec. & Obst.* **43**:343, 1926.

10. Simmons, C.: The Treatment of Oral Cancer, *Am. J. Roentgenol.* **26**: 5, 1931.

as living and free from disease after five years. Simmons' report would have been of real value had he included the results in the patients with metastases at the time of admission as well as those in the patients with cancer in hopelessly advanced stages.

Steiner's<sup>2</sup> report, published almost twenty years ago, included a series of thirty-three consecutive unselected cases. Seventeen of the patients were operated on, and three (9 per cent) remained free from disease for three years. At various times, Morestin<sup>11</sup> reported twenty-six cases with operation, with three (11 per cent) of the patients free from disease for three years. Boyd and Unwin<sup>12</sup> reported that four of ten patients were apparently cured three years after operation. The following authors reported a total of seventy-nine cases with no cures: Warren,<sup>13</sup> eight; Brewer,<sup>5</sup> eleven; Bradfield,<sup>14</sup> seven, and Davis,<sup>2</sup> fifty-three. All the aforementioned reports, except Steiner's, were based on groups of cases selected because of operability, and are therefore of no value from the comparative standpoint.

The published results obtained from irradiation, or from a combination of irradiation and surgical intervention, are much more encouraging. Schreiner and Simpson,<sup>15</sup> using irradiation only, reported thirty cases, among which were six cures (20 per cent) at the end of five years. Regaud<sup>16</sup> reported 19 per cent of cures at the end of five years among forty-seven patients treated by irradiation, and Berven,<sup>17</sup> twenty-one among eighty-one patients (26 per cent) who were free from disease for five years or longer.

The results obtained in the ninety-nine cases of this study are tabulated in table 5. Of the entire group, twenty-eight patients have now been free from disease for from five to eight years.

11. Morestin, H.: Cancer de la commissure labiale et de la joue: Ablation avec résection d'une moitié du maxillaire inférieur: Autoplastie, Bull. et mém. Soc. anat. de Paris 78:476, 1903; Cancer de la joue, *ibid.* 80:454, 1905; Neuf cas de cancer de la joue, *ibid.* 81:98, 1906; Resultats éloignes d'operations pour cancers de la face interne de la joue, Bull. et mém. Soc. d. chirurgiens de Paris 34:1058, 1908; Cancer de la joue, *ibid.* 39:1186, 1913.

12. Boyd, S., and Unwin, W. H.: On a Series of Cases of Cancer of the Mouth and Fauces, Practitioner 72:397, 1904.

13. Warren, J. C.: Cancer of the Mouth and Tongue, Ann. Surg. 48:481, 1908.

14. Bradfield, E. W. C.: Anoci-Association and Cancer of the Cheek, Indian M. Gaz. 49:141, 1914.

15. Schreiner, B. F., and Simpson, B. T.: Five Year End-Results of Radiation Treatment of Cancer of the Oral Cavity, Nasopharynx and Pharynx, Radiol. Rev. & Chicago M. Rec. 51:327 (Aug.) 1929.

16. Regaud, C.: Les épithéliomes de la cavité buccale: leur traitement par le radium et les rayons X, J. de méd. et chir. prat. 103:15, 1932.

17. Berven, E.: Development of Technique and Results of Treatment of Tumors of the Oral and Nasal Cavities, Am. J. Roentgenol. 28:332, 1932.

These figures were based on a representative group of patients with carcinoma of the cheek admitted to the Memorial Hospital. In this group are included the patients with advanced disease who were admitted for palliative treatment and for observation. In about 70 per cent of the cases with fatal outcome, the patient died within one year after the first symptom, death in one instance occurring within four months. The case of longest duration among these patients was one of two and one-half years.

The primary lesion was controlled in forty-six cases, or in almost one half of the total number, so that the patients either remained free from disease or died of metastases without the local recurrence of the primary lesion. With the exclusion of the cases of advanced disease in which palliative treatment only was given, we succeeded in controlling the

TABLE 5.—*Results at the End of Five Years in the Ninety-Nine Cases of Cancer of the Cheek*

Status of Patient	Number
Dead as result of cancer of cheek.....	57
Lost track of with disease (probably dead).....	3
Living with recurrence of primary lesion.....	1
Total number of failures in treatment.....	61
Indeterminate group	
Dead as result of other causes and without recurrence.....	5
(two after one year; two after two years and one after four years)	
Lost track of, without recurrence.....	3
(one after one year; one after two years, and one after four years)	
Total number of indeterminate results.....	8
Total number (99) minus those of indeterminate group.....	91
Free from disease after from five to eight years.....	28
Cures after five years.....	30 per cent.

primary lesion in forty-nine of sixty-seven (73 per cent) attempts at cure. It is therefore evident that once the disease has metastasized to the neck, its control becomes far more difficult.

Although the 30 per cent of cures at the end of five years is not satisfactory, it is a marked improvement over the results noted in most surgical statistics. Surgical intervention in carcinoma of the cheek is distinctly a major procedure. The operative mortality is high (Steiner, 11 per cent; Warren, 25 per cent). Morestin, Davis, Brewer, Steiner, Polya and others described extensive plastic operations which included the excision of all of the soft parts of the cheek, as well as a submaxillary dissection. All of these writers emphasized the necessity of wide removal of the soft parts of the cheek. The deformity is great, and ankylosis of the jaws from cicatricial contraction of the cheek is common. To avoid this complication, Morestin and Warren recommended excision of one-half the mandible in all of these cases, and

the former stated that in one case of early cancer of the cheek, the extent of the operation which he performed "provoked a veritable stupor in the assistants and in the patient's own physician." The outcome was, however, successful, and at the time of the report, the patient had been cured of the disease for two years.

In our opinion, the most successful method of treatment of cancer of the cheek is a combination of irradiation and surgical intervention. The treatment of the primary lesion and of the cervical metastases should be considered as separate problems. Irradiation is preferable to surgical treatment for the control of the primary lesion.

Prophylactic neck dissection is not justified. The method of treatment of cervical metastases should be selected to suit the individual patient and may be by surgical means alone, by irradiation alone or by a combination of the two procedures.

#### SUMMARY

1. An unselected series of ninety-nine cases of cancer of the cheek is subjected to critical analysis.

2. The methods of treatment employed are discussed in detail.

3. The net results at the end of five years show 30 per cent of the patients living and free from disease.



# OSTEOGENESIS

## AN EXPERIMENTAL STUDY

J. DEWEY BISGARD, M.D.

OMAHA

The genesis of bone, the palimpsest of the evolution of man, remains to this day undetermined and a subject of much controversy. This controversy involves not only the fundamental problems of the chemical processes of ossification but also its histogenesis. Without established knowledge of the rôle (if any) played by tissue cells in the laying down of bone and of the specialization required of cells for such a function, the part played by such tissues as the periosteum, endosteum, cartilage and granulation tissue can only be conjectured. However, I have presented experimental results which indicate that the periosteum is particularly conducive to the deposition of new bone on its cambium surface.

Probably no other problem in histologic physiology has been investigated so extensively and has given rise to more conflicting results. From a review of the literature, it is apparent that much of the conflict and confusion has arisen from the error of making direct comparison of experimental results without adequate appreciation of the wide differences in osteogenic response brought about by the multitudinous minor individual variations in experimental procedure. Among the factors which exert great influence are: (1) the age of the subject, (2) the type of bone (spongy or dense), (3) the nutrition of both the bone and the periosteum (the normal variations in different parts of the body and the changes brought about by experimental procedure), (4) the operative technic used in the handling of the tissues (hemostasis, trauma, etc.), (5) the extent of the stimulus resulting from function and (6) the degree of immobilization. Evidence of the influence exerted by some of these factors has been brought out in my investigation.

### METHOD AND MATERIAL

With one exception, young dogs were used for all experiments. One old animal was utilized to demonstrate the influence of the age of the subject on the osteogenic response of the tissues.

All observations were made on the ribs and their cartilages and the costal periosteum and perichondrium, for the following reasons:

1. Each costal arch is a dispensable individual unit which can be removed in its entirety without causing appreciable dysfunction. For

---

From the Department of Surgery, University of Michigan.

the same reason and on account of the multiplicity of the ribs, it was possible to utilize each animal for several experiments.

2. The rich blood supply of both the rib and its periosteum and the cancellous structure of the rib provide circumstances optimally favorable to osteogenesis.

3. Continuous respiratory excursions and stresses after operation contribute uninterrupted functional stimuli to osteogenesis.

The operative procedures were carried out with ether anesthesia and with rigid aseptic surgical technic. Although each dog was the subject of several experiments, each procedure was performed independently of the others, through a separate incision, one costal segment always being left undisturbed between the operative sites.

All of the wounds healed by primary intention. The animals were killed from sixty-five to ninety-three days after operation and the hemithoracic walls which were operated on were removed *en masse*; roentgenograms were made, and the individual specimens were removed for gross and microscopic study.

Since each experimental procedure was repeated in two or more dogs, and since more than one experiment was carried out in each animal, each problem and its results will be presented in logical sequence, and a brief protocol for each animal is given in the accompanying table.

#### THE PERIOSTEUM. IS IT ONLY A LIMITING MEMBRANE?

In each experiment the periosteum was elevated carefully from the rib with a dull instrument in an effort to obtain cleavage which would not detach small fragments of bone with the periosteum. Care was exercised to obtain good hemostasis, to avoid damage to the intercostal blood vessels and nerves and to minimize trauma of the periosteum.

EXPERIMENT 1 (dogs 70, 71 and 72).—*Subperiosteal removal of the entire rib.*

In each of these dogs an entire rib was removed subperiosteally; it was disarticulated from the vertebra posteriorly and from the costal cartilage anteriorly, leaving the periosteum undisturbed except for the excision of a long, narrow strip for use in the control experiment, described subsequently (experiment 9; diagram 1, fig. 1).

Roentgenograms of the specimens obtained eighty-five days after operation are reproduced in figure 2 *D*, 3 *C* and 4 *B*. In each instance a large quantity of new bone was deposited in the periosteal bed, irregularly replacing the original rib. The breaks in continuity shown in figure 4 *B* probably represent fractures of the newly formed rib.

Both grossly and microscopically there was a continuous ribbon of new bone extending from the costal cartilage to within a short distance

of the vertebra. The regenerated rib was thin and irregularly nodular and consisted of segments with normal costal architecture (fig. 5) separated by small segments composed of newly formed cartilage and newly formed bony trabeculae.

EXPERIMENT 2 (dogs 17 G and 18 G).—*Subperiosteal removal of the entire rib and its cartilage.*

To preclude the possibility encountered in the first experiment that the regenerated rib might arise from the costal cartilage the same procedure was repeated in two dogs with the additional resection of the costal cartilages. The rib was disarticulated from its vertebral attachment and with its cartilage was unsheathed and resected to the sternum (diagram 2, fig. 1).

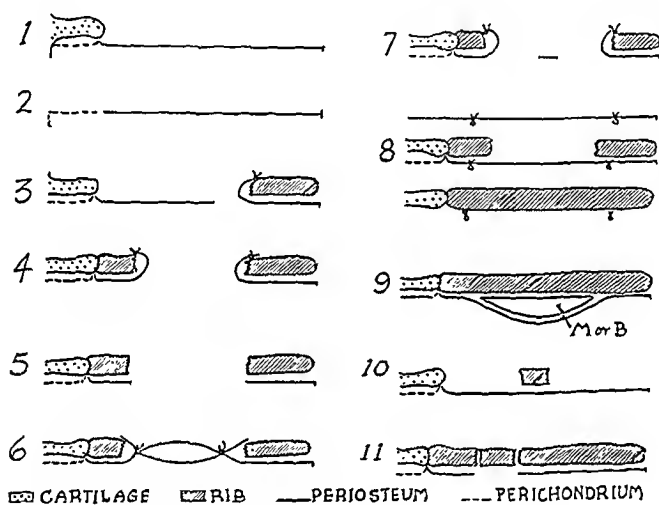


Fig. 1.—Diagrams illustrating the technic of several of the experiments: 1, experiment 1; 2, experiment 2; 3, experiment 3; 4, experiment 4; 5, experiment 5; 6, experiment 6; 7, experiment 7; 8, experiment 11; 9, experiments 13 and 14; 10, experiment 16, and 11, experiment 17. *M* or *B* denotes the muscle or the rubber bag interposed between the periosteum and the rib.

A narrow strip of periosteum was resected for use in the control experiment (experiment 9).

Both animals were killed eighty-six days after operation. The postmortem roentgenogram of dog 17 (fig. 6 *A*) shows that the rib regenerated irregularly and incompletely up to but not beyond the periosteoperichondrial junction. From this point to the sternum there is no shadow of greater density than that of soft tissue.

Macroscopically, these regenerated ribs were nodular, irregularly shaped, broader, thinner and more pliable than a normal rib. The perichondrial bed had the consistency and appearance of fascia. Nowhere did it contain tissue with skeletal rigidity.

The microscopic appearance of the regenerated rib was essentially the same as that described in experiment 1. The new bone apparently had developed both by direct and by enchondral osteogenesis. The perichondrium consisted of a layer of dense fibrous tissue several times its original thickness. In it were small scattered nodules of cartilage which, when treated with Mallory's connective tissue stain, proved to be fibrocartilage.

EXPERIMENT 3 (dog 7).—*Subperiosteal resection of the anterior half of the rib with exclusion of the end of the posterior costal stump.*

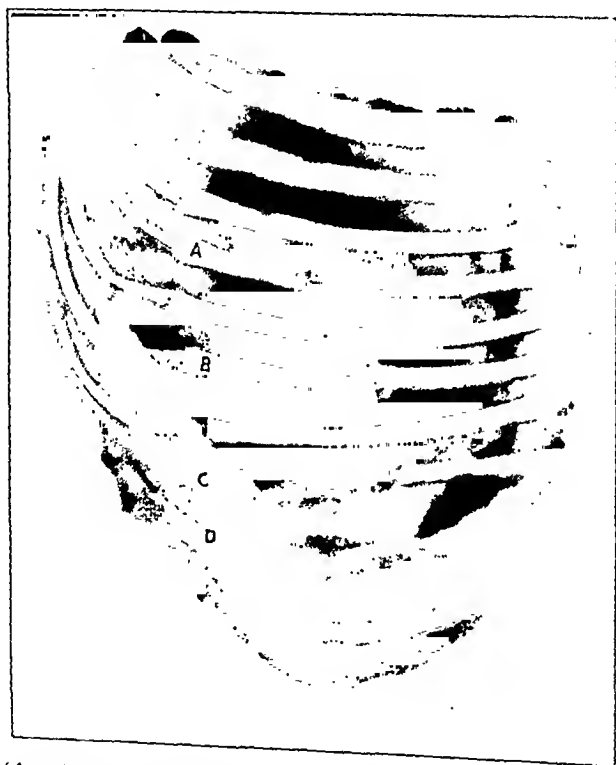


Fig. 2 (dog 70).—*A* indicates the periosteum only, zenkerized (experiment 15 B); *B*, the interposition of the costal cartilage (experiment 17; fig. 1, diagram 11); *C*, the posterior costal stump sealed with a periosteal flap (experiment 3; fig. 1, diagram 3), and *D*, a subperiosteal excision of the entire rib (experiment 1; fig. 1, diagram 1).

From the posterior portion of the periosteal bed which was left after subperiosteal resection of the anterior half of the rib, a pedicle flap of periosteum was dissected from the pleura and intercostal structures and sutured tightly over the end of the posterior costal stump so as to seal it completely (diagram 3, fig. 1).

A narrow strip of periosteum was removed for the control experiment (experiment 9).

The duration of the experiment was eighty-five days. As illustrated in the roentgenogram (fig. 2 C) regeneration occurred along the entire periosteal bed, but in the area from which the periosteal flap had been raised no shadow of bone is discernible.

Microscopic examination verified these roentgenologic findings. The regenerated segment presented a picture similar to that described in experiment 1. The old bone of the severed end of the costal stump for a short distance posteriorly was necrotic and was undergoing

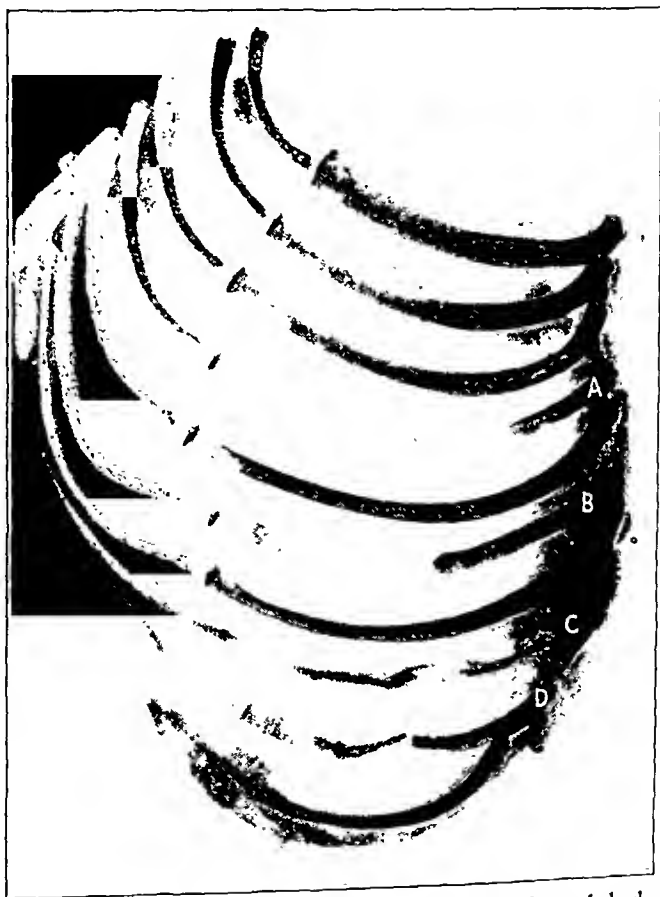


Fig. 3 (dog 71).—*A* indicates the devascularized periosteal bed (experiment 11; fig. 1, diagram 8); *B*, the periosteum, zenkerized (experiment 15 B); *C*, the subperiosteal excision of the entire rib (experiment 1; fig. 1, diagram 1), and *D*, the isolated segment of the periosteum (experiment 6; fig. 1, diagram 6).

absorption and replacement by new bone. Over its surface and between it and the periosteal flap there were considerable newly formed cartilage and bony trabeculi.

EXPERIMENT 4 (dog 72).—*Subperiosteal resection of a costal segment 7 cm. in length; isolation of both ends of the rib with periosteal flaps.*

The periosteal tube between the severed ends of the rib was carefully dissected from the intercostal structures and from the pleura and

divided into two flaps which were turned and sutured tightly over the ends of the costal stumps, so that only pleura formed the floor of the decostalized bed. The procedure is illustrated in diagram 4, figure 1.

A small piece of periosteum was excised for the control experiment (experiment 9).

The roentgenogram (fig. 4 *A*) of the postmortem specimen obtained eighty-three days after operation presents shadows of newly deposited bone covering the severed ends of the rib and complete absence of bone in the space intervening between the costal stumps.

These findings were verified by macroscopic and microscopic observations. The microscopic picture is illustrated in figure 7. The

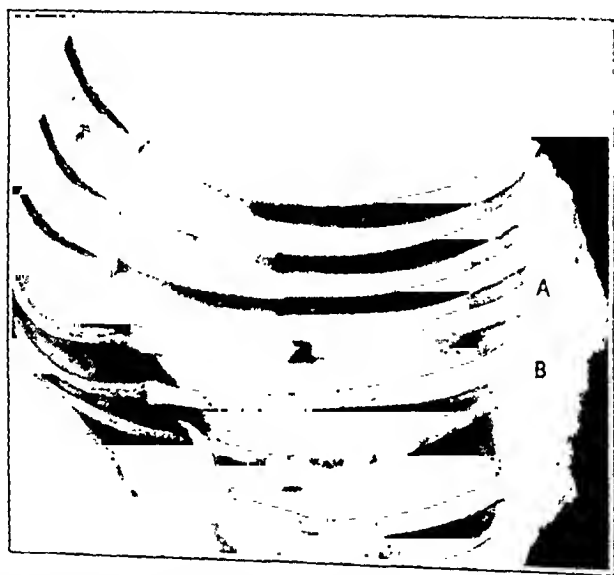


Fig. 4 (dog 72).—*A* indicates the deperiostealized bed; the costal stumps are sealed with periosteal flaps (experiment 4; fig. 1, diagram 4). *B* indicates the subperiosteal resection of the entire rib (experiment 1; fig. 1, diagram 1).

free ends of both ribs contained necrotic old bone which was undergoing transformation; they were covered by a layer of newly formed bone, osteoid tissue and cartilage. This new formation was sharply delimited by the periosteal caps. The space between the costal stumps was bridged by fibrous tissue only.

**EXPERIMENT 5 (dogs 78 and 18 G).**—*Resection of 7 cm. of both the rib and its periosteum.*

After removal of the costal segment subperiosteally, the periosteum was dissected from the intercostal structures and pleura and was excised so that only pleura formed the floor of the gap between the ends of the rib (diagram 5, fig. 1).

A portion of the excised periosteum was decalcified and sectioned for study in the control experiment (experiment 9).

A roentgenogram of a sixty-seven day specimen (fig. 8 *A*) shows proliferation of new bone about the costal ends, particularly the anterior one, but no evidence of bone in the gap between the stumps.

As in the experiments described earlier, microscopic study revealed necrotic old bone at the free ends of the costal stumps which was undergoing replacement by creeping substitution. They were capped

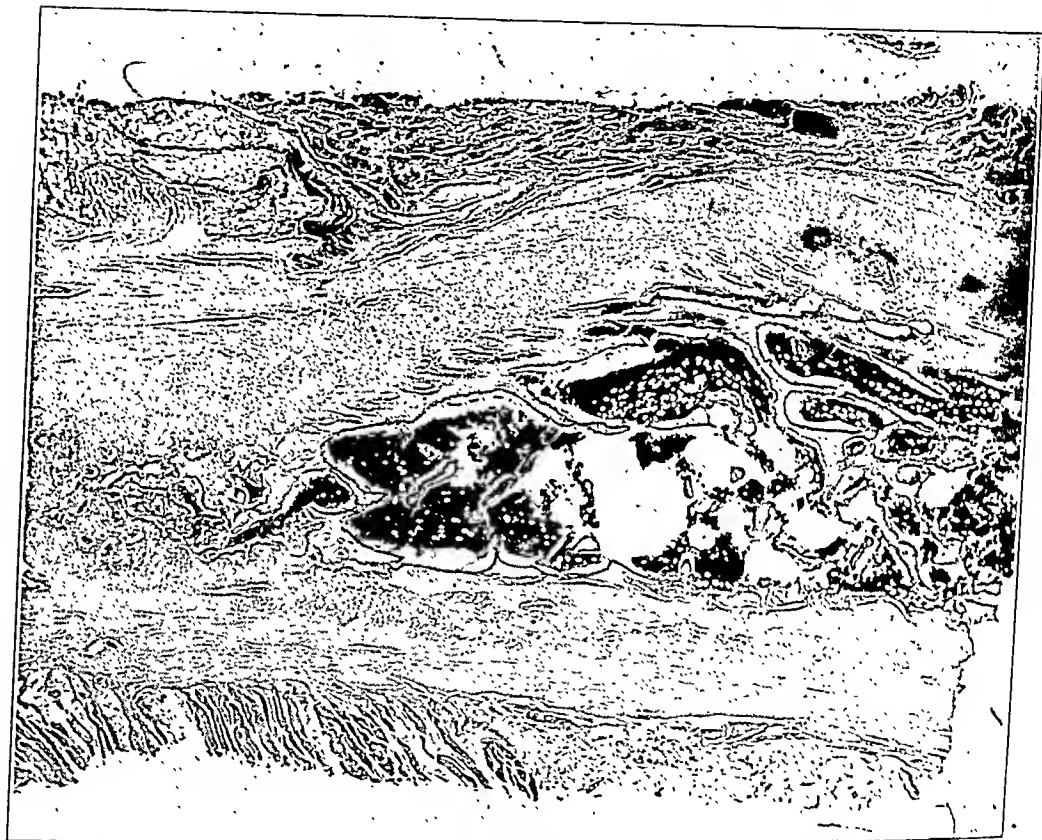


Fig. 5.—A low power photomicrograph of the regenerated costal segment referred to in experiment 1. Note the reproduction of the normal costal architecture.

by a layer of new bone which closed the open medullary spaces. There was evidence of enchondral osteogenesis. Neither bone nor cartilage was found in the tissue intervening between the costal stumps; only fibrous tissue was present.

EXPERIMENT 6 (dog 71).—*Isolation of a segment of periosteum in its normal bed.*

The ends of the periosteal tube which was left after the subperiosteal resection of a costal segment approximately 7 cm. in length were closed tightly around the ends of the costal stumps with encircling

sutures of heavy silk carefully placed to avoid damaging or including the intercostal vessels. Thus the ends of the rib were sealed, and a segment of periosteum was isolated (diagram 6, fig. 1).

A narrow strip of periosteum was excised for study in the control experiment (experiment 9).

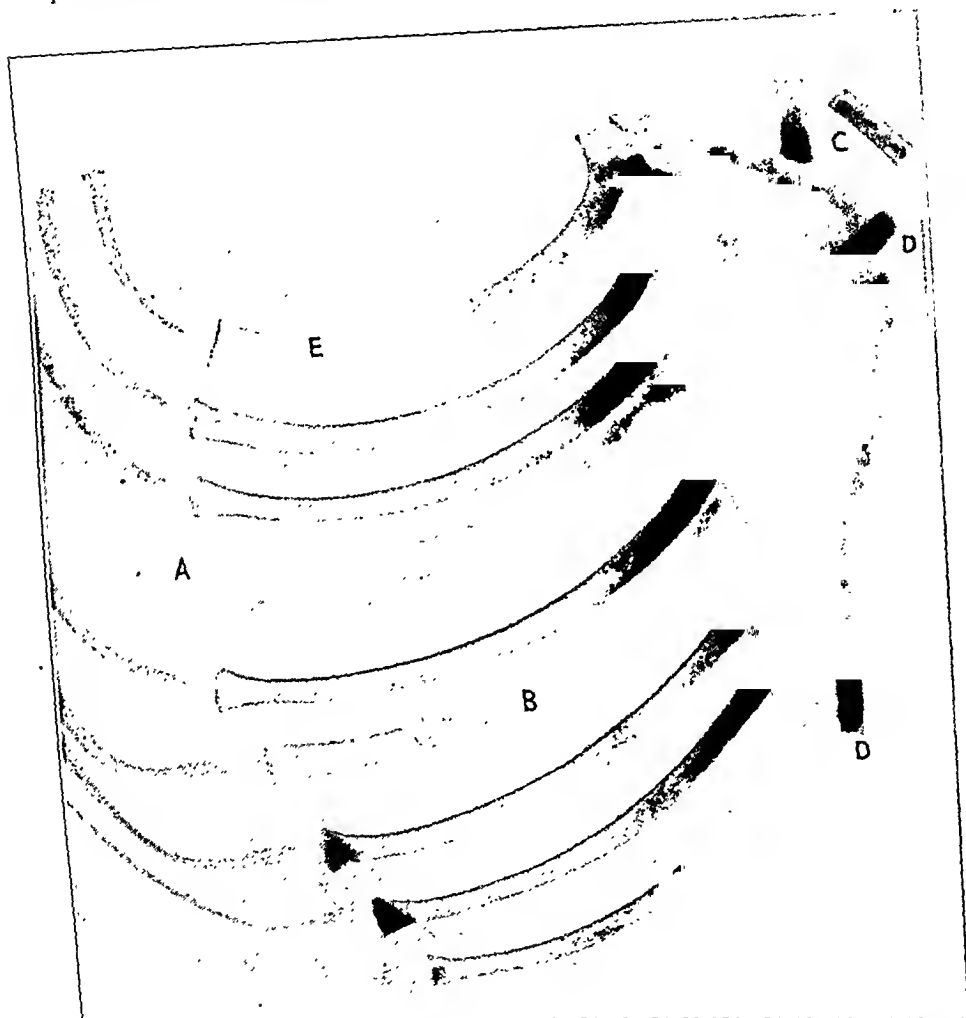


Fig. 6 (dog 17).—*A* indicates the subperiosteal and subperichondrial resection of the entire rib and its cartilage (experiment 2; fig. 1, diagram 2); *B*, the costal stumps only, zenkerized (experiment 15 A); *C*, the transplanted costal segments (experiment 18 A); *D*, the transplanted zenkerized costal segments (experiment 18 C), and *E*, a costal segment excised post mortem for purposes of comparison with the costal stumps of the experimental specimens (the latter in contrast show rounded edges from absorption and the deposition of new bone).

The result of this experiment eighty-five days after operation is shown in the roentgenogram (fig. 3 *D*). Extensive absorption of the costal ends had taken place, and in the space intervening between and



isolated from the costal stumps there was a well formed segment of bone which corresponded to the isolated segment of the periosteal bed.

On gross examination there were three distinct pieces of bone separated by two white scars which stood out sharply on the inner surface of the periosteum.

Microscopically, the ends of the costal stumps contained necrotic old bone which was invaded by granulation tissue and was undergoing absorption and some newly formed bony trabeculi. On the surface of

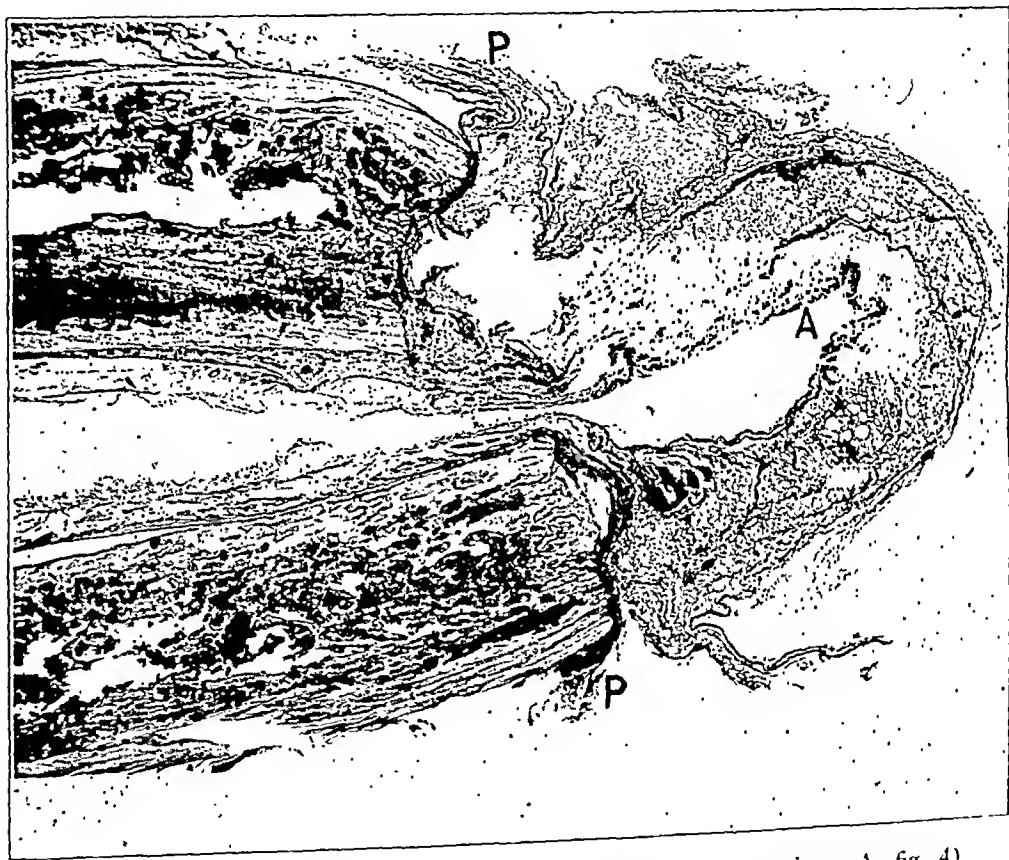


Fig. 7.—A low power photomicrograph (experiment 4; specimen A, fig. 4), showing the costal stumps covered with flaps of periosteum (*P*) turned back from the decostealized bed and sutured tightly over both ends of the rib. The space (*A*) between the costal stumps from which both bone and periosteum have been entirely removed is filled with young fibrous tissue. It contains neither new bone nor cartilage. Note the new bone between the ends of the rib and the periosteum which covers them.

the isolated periosteal segment was a well formed piece of bone. Between it and the ends of the rib there were spaces filled with young fibrous tissue and foci of chronic inflammation with many foreign body giant cells surrounding small bits of silk thread. A photomicrograph of the specimen is shown in the lower illustration of figure 10.

It is probable that the foreign body reaction was responsible for the extensive absorption of the ends of the rib.

EXPERIMENT 7 (dogs 77 and 186).—*Isolation of a segment of periosteum.*

After subperiosteal resection of 9 cm. of a rib, a small segment of periosteum in the center of the periosteal bed was left undisturbed, and the remainder of the membrane was raised from the pleura and inter-



Fig. 8 (dog 78).—A indicates a complete resection of both the costal segment and its periosteum (experiment 5; fig. 1, diagram 5).

costal structures and sutured as two pedicle flaps over the ends of the costal stumps in diagram 7, figure 1.

Small pieces of periosteum were also excised for the control experiment (experiment 9).

In the roentgenogram of the specimen obtained sixty-seven days after operation (fig. 9 C) there is seen an irregular shadow of newly deposited bone in the area occupied by the isolated segment of periosteum.

These findings were substantiated by gross examination.

The ends of the rib were shown by microscopic study to contain necrotic bone and trabeculi of new bone, the latter sealing the exposed cancellous spaces. New bone and cartilage filled the spaces between the ends of the stumps and the periosteum covering them. The space between the two stumps was bridged with a layer of fibrous tissue containing a small island of new bone (fig. 10 *A*).

EXPERIMENT 8 (dogs 70, 77, 78 and 18 G).—*Free transplantation of periosteum.*

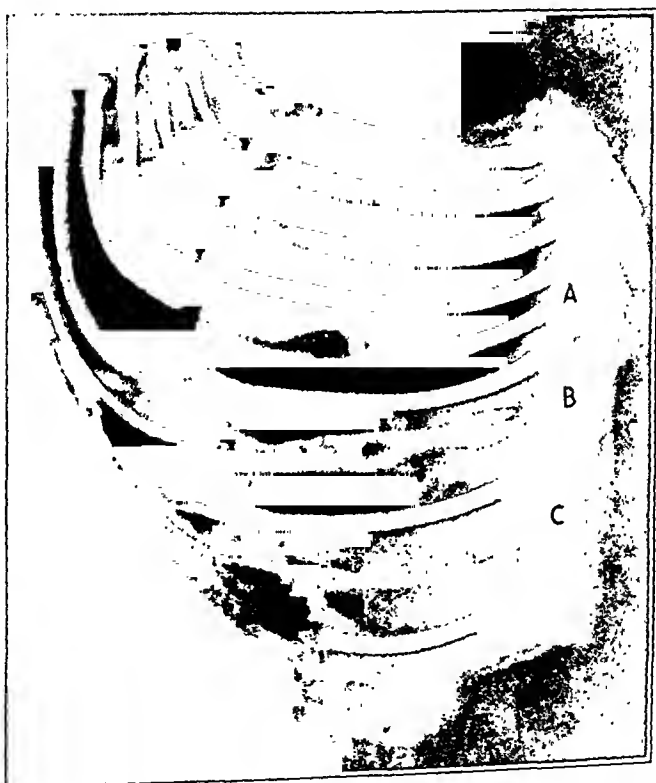


Fig. 9 (dog 77).—*A* indicates both the periosteum and the ends of the rib, zenkerized (experiment 15 C); *B*, a subperiosteal resection of the entire rib except for a small segment (experiment 16; fig. 1, diagram 10), and *C*, an isolated segment of the periosteum, the ends of the costal stumps being sealed with periosteal flaps (experiment 7; fig. 1, diagram 7).

In four young dogs strips of periosteum to which small linen sutures were attached for identification were transplanted to the erector spinae muscles.

At postmortem examination from sixty-seven to eighty-six days later two of the transplants could not be found, but the two which were recovered contained (fig. 11 *a*) small nodules of new bone encapsulated in fibrous tissue. In two or three areas fibers of thread were surrounded by a zone of active inflammation. In neither specimen

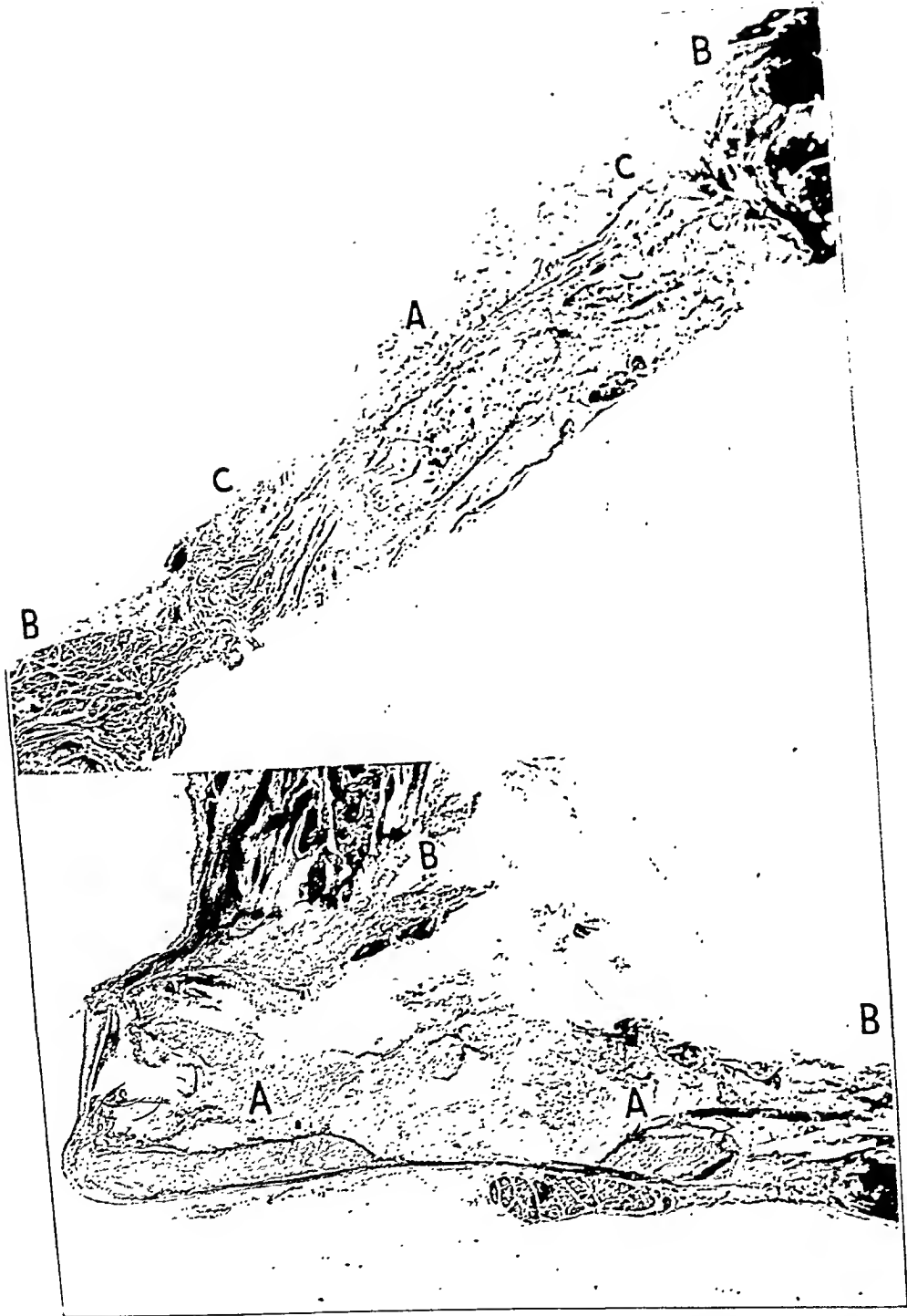


Fig. 10.—The upper illustration is a low power photomicrograph of specimen *C* shown in figure 9 (experiment 7), showing the island of new bone (*A*) which has been deposited on the isolated segment of periosteum between the costal ends (*B*). The two periosteal flaps which were raised from the bed at *C* to isolate the central segment (*A*) can be seen sealing the costal stumps (*B*). Note that the new bone has not extended into the deperiostealized areas (*C*). The technic is shown in figure 1, diagram 7. The lower illustration is the low power photomicrograph of the specimen shown in *D*, figure 3 (experiment 6). Note the islands of new bone (*A*) in the periosteal bed which was isolated from both costal stumps (*B*), with encircling sutures which sealed the ends of the rib. The operative procedure is illustrated in figure 1, diagram 6.

was there old bone or evidence to suggest that fragments of bone had been transplanted with the periosteum. There was no cartilage, and consequently no direct indication of endochondral osteogenesis.

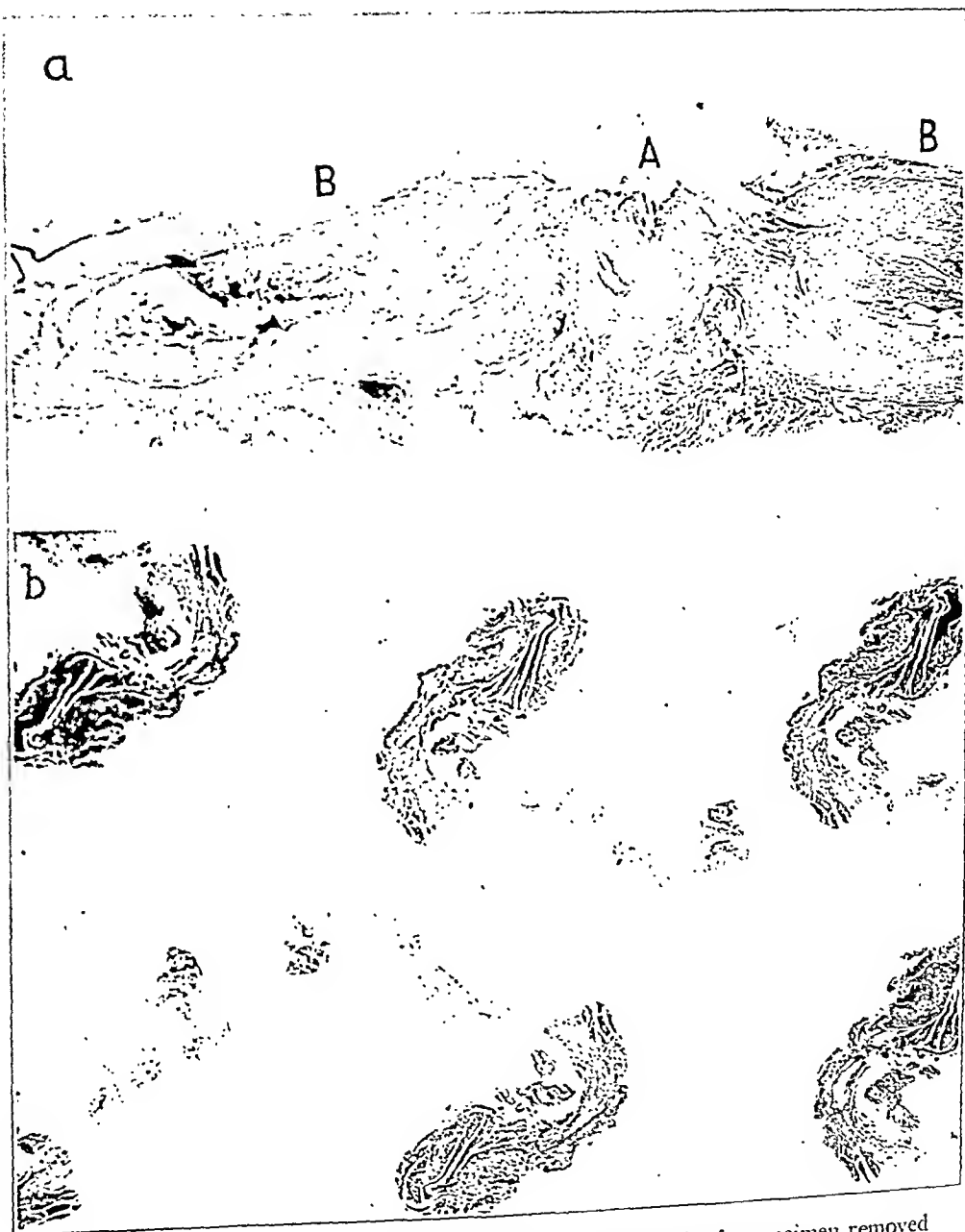


Fig. 11.—In *a* is presented a low power photomicrograph of a specimen removed from dog 77 (experiment 8). In the encapsulated piece of periosteum which had been transplanted to the erector spinae muscles, two nodules of new bone (*B*) were found. The inflammatory tissue (*A*) surrounds fibers of the linen thread suture which were buried with the transplant to aid identification. In *b* are shown serial sections of one of the fresh strips of periosteum used in experiment 9. This illustrates the method of investigating the control material.

## EXPERIMENT 9.—Control.

Some of the investigators who believe that the periosteum has no specific osteogenic potentialities have suggested that the new bone which is laid down in periosteal beds or on periosteal transplants may arise from small fragments of bone which adhere to and are transplanted with this membrane. In an attempt to test this contention and to obtain as much control data as possible, fourteen narrow strips of periosteum were excised from the periosteal beds of eight animals after subperiosteal resection of the costal segments. These have been noted in experiments 1, 2, 3, 4, 5, 6, 7, 10 and 17. Each strip was decalcified and cut into innumerable serial sections, and many were mounted for study as illustrated in figure 11 *b*. In only one of the fourteen specimens was bone found.

THE INFLUENCE OF CERTAIN FACTORS ON THE OSTEOGENIC  
RESPONSE OF THE PERIOSTEUMEXPERIMENT 10 (dog 16 G).—*Influence of age.*

Three of the experiments with young animals reported earlier were repeated in an obviously aged dog.

*A. Subperiosteal resection of an entire costal unit, as in experiment 2.*

A small strip of the periosteum was removed to be used in experiment 9. The roentgenographic (fig. 12 *B*), gross and microscopic examination of the specimen obtained ninety-three days after operation showed no evidence of costal regeneration. There was no new or old bone or cartilage, the periosteum and perichondrium consisting of thickened pliable bands of dense fibrous tissue. Compare these findings with those reported in experiment 2 and the roentgenogram illustrated in figure 6 *A*.

*B. Subperiosteal resection of a costal segment leaving small costal stumps.*

In the roentgenogram (fig. 12 *A*) there can be seen no evidence of costal regeneration. The periosteal bed consisted entirely of fibrous tissue. The ends of the rib contained both necrotic bone undergoing absorption and a few trabeculae of new bone on the surface. Compare these results with the roentgenographic and other findings reported in the experiments with young animals.

*C. Free transplantation of the periosteum.*

Three strips of periosteum were transplanted to the erector spinae muscles with attached linen ligatures for identification. Two of the specimens were recovered at postmortem examination and consisted of firm, fibrous nodules which on section were found to be composed solely of fibrous tissue with an active chronic inflammatory reaction around bits

of thread in a few areas. There was no bone or cartilage. Compare these findings with those reported in experiment 8.

EXPERIMENT 11 (dogs 71 and 18 G).—*Circulatory influence.*

After resecting 7 cm. of a rib subperiosteally in each animal, the intercostal vessels were ligated 2 cm. distal and proximal to the ends

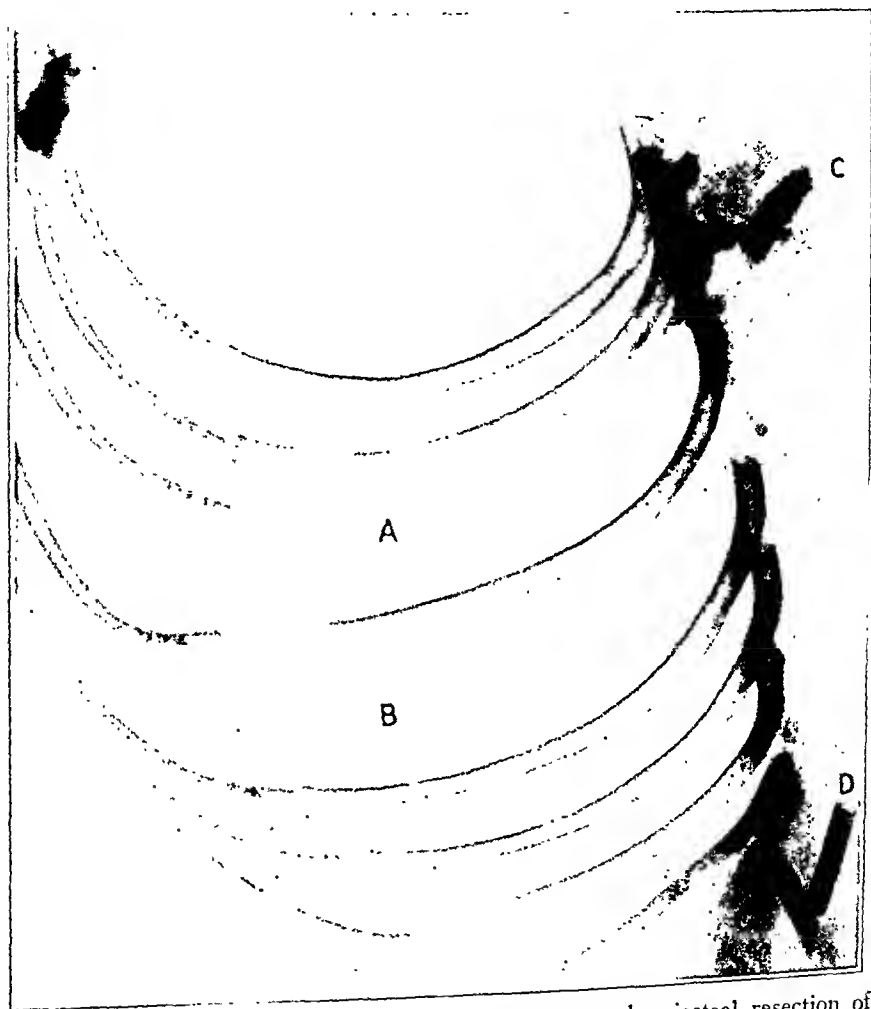


Fig. 12 (dog 16, an aged animal).—*A* indicates a subperiosteal resection of a long costal segment, leaving small stumps; *B*, a subperiosteal and subperichondrial resection of the entire rib and its cartilage. Note in both *A* and *B* complete absence of costal regeneration from the periosteum and costal stumps of this old animal. Compare with similar experiments in young animals shown in the preceding roentgenograms. *C* indicates free costal transplant, and *D*, free zenkerized costal transplants.

of the decostalized bed. In an endeavor to impoverish further the blood supply to the part by interrupting a portion of the collateral circulation, the vessels accompanying the rib above and the one below were ligated at both extremities in the same plane as those of the resected

segment. The principle of the procedure is illustrated in diagram 8, figure 1.

The result eighty-five days after operation is shown in the post-mortem roentgenogram of one of the animals (fig. 3 *A*). Apparently no new bone was deposited on this devascularized segment of periosteum.

Microscopically the tissue was entirely fibrous, and there was no trace of bone or cartilage. The ends of the costal stumps contained much necrotic old bone, which was undergoing revascularization and absorption. New bone had been deposited on the surface and in the revascularized spaces.



Fig. 13 (dog 80).—*A* indicates the periosteal bed, curetted and rubbed vigorously with gauze. Note that the deposition of new bone extends for a short distance beyond the end of the anterior stump and that the rest of the decostalized bed contains only one small island of bone. *B* indicates free costal transplants in muscle.

#### EXPERIMENT 12 (dogs 80 and 76).—*Influence of trauma.*

A 9 cm. decostalized periosteal bed was curetted and rubbed vigorously with gauze to remove the cambium layer.

The roentgenogram of one of the specimens sixty-five days after operation is shown in figure 13 *A*. Considerable new bone was deposited for a short distance beyond the end of the anterior costal stump, but throughout the remainder of the periosteal bed there is seen only one small nodule of new bone.

Macroscopic and microscopic examinations were confirmatory. The new bone appeared to arise at least partially by enchondral osteogenesis.



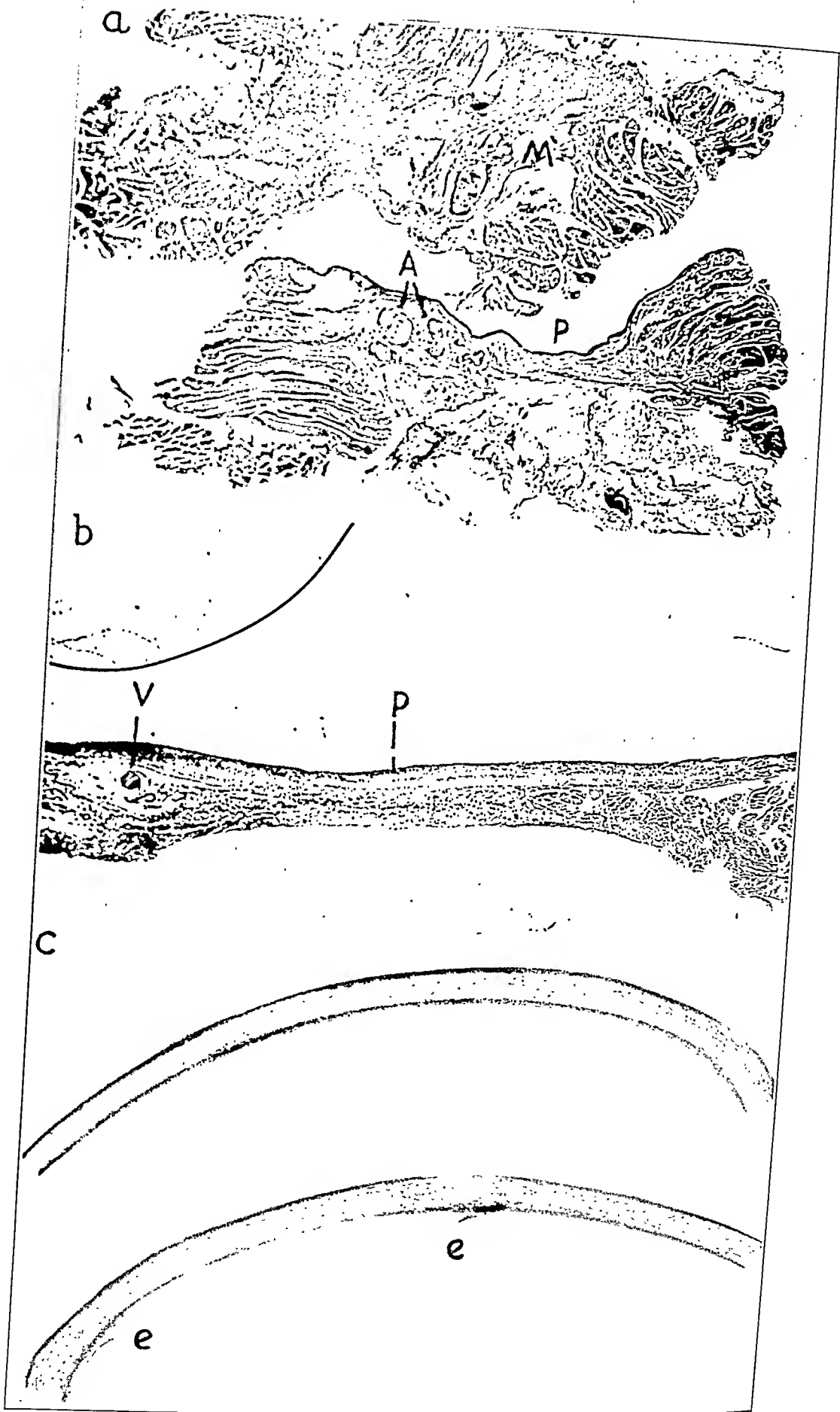


Figure 14

## EXPLANATION OF FIGURE 14

Fig. 14.—In *a* (dog 84), is presented a low power photomicrograph of the specimen obtained in experiment 13, showing the pedicled transplant of muscle (*M*) interposed between the rib and its periosteum (*P*). The intercostal vessels and nerve are labeled *A*. Note that no new bone has been deposited on the periosteal surface (*P*). In *b* (dog 81), is presented a low power photomicrograph of a specimen obtained in experiment 14. The inflammation resulting from the rubber bag interposed between the rib and its periosteum has resulted in marked thickening of the periosteum (*P*). The intercostal vessels and nerve are labeled *V*. Note that no new bone has been deposited on the surface of the periosteum. In *c* (dog 84F), is presented a postmortem roentgenogram of two ribs obtained in experiment 13, showing nodules of new bone (*C*) deposited in the angle between the rib and the periosteum. In the space between these two nodules the periosteum was separated from the rib by the interposed muscle.

EXPERIMENT 13 (dog 84 F).—*Influence of apposition of muscle.*

With a technic similar to that of pneumolysis of the pectoral muscle described by John Alexander,<sup>1</sup> long segments of four contiguous ribs were stripped of their periosteal sheaths, and a muscle flap which had been raised from the thoracic wall and had been fashioned with an adequate vascular pedicle was insinuated between the internal surface of the bare ribs and the mesially displaced periosteum and intercostal bundles. The technic is illustrated in diagram 9, figure 1.

The animal was killed sixty days after operation. As illustrated in figure 14a, no new bone had been deposited on the surface of the periosteum. The contacting muscle was loosely adherent to the periosteum in some areas and densely adherent in others. In the angles between the rib and the periosteum at both borders of the interposed muscle small nodules of bone had been deposited (fig. 14c).

EXPERIMENT 14 (dogs 81 and 82).—*Influence of apposition of foreign body.*

The procedure, a pneumolysis, which has been described in experiment 13, was repeated in two dogs, with the exception that the space between the ribs and the periosteum was filled with a rubber bag instead of muscle. The rubber bag consisted of a surgeon's glove filled with sterile salt solution. Recurring accumulations of serum in the subcostal space bulged the healed incision and necessitated repeated aspirations.

No infection occurred, and the animals were killed sixty-two and sixty-five days after operation. Each bag had become encapsulated by a thick layer of fibrinous exudate.

Microscopic examination revealed that the denuded ribs were entirely necrotic, and that the periosteum and pleura (fig. 14b) were markedly thickened and presented an active inflammatory reaction. Nowhere on the surface of this inflammatory membrane could bone be palpated, and none was found in the sections studied.

EXPERIMENT 15.—*Influence of chemical cauterization.*

A. (dogs 76 and 17 G).—*Costal stumps only treated with Zenker's solution, the periosteum being carefully guarded from contact with the solution.*

The roentgenogram of one of the specimens (fig. 6B) obtained eighty-six days after operation indicates that new bone was irregularly deposited in the periosteal bed.

On palpation the segment was semirigid throughout and contained scattered hard nodules.

1. Alexander, John: Supraperiosteal and Subcostal Pneumolysis with Filling of Pectoral Muscle, Arch. Surg. 28:538 (March) 1934.

Microscopically the ends of both the costal stumps were necrotic and contained no new bone. In the decostalized bed there were segments of new bone with well formed costal architecture and nodules containing cartilage, bony trabeculae and osteoid tissue.

*B. (dogs 70 and 71).—Periosteum only treated with Zenker's solution.*

This experiment repeated the procedure of 13 *A*, with the exception that only the periosteum was treated with Zenker's solution. The ends of the rib were covered with bone wax while the solution was being applied to the periosteal bed.



Fig. 15 (dog 70).—A low power photomicrograph of specimen *B* shown in figure 2 (experiment 17). New bone proliferating from the ends of the costal stumps has invaded and replaced much of the interposed segment of cartilage and has established bony union. Note the marked density of some of the new bone. The experimental operative technic is illustrated in figure 1, diagram 11.

The roentgenograms (figs. 2 *A* and 3 *B*) of the specimens obtained sixty-five days after operation show no evidence of bone in the zenkerized periosteal beds.

Neither cartilage nor bone was found on microscopic examination. The tissue was entirely fibrous. The ends of the rib contained both old dead bone and newly formed bone and cartilage, some of the new bone apparently arising by enchondral osteogenesis.

*C. (dogs 77 and 76).—Both the periosteum and the costal stumps treated with Zenker's solution.*

The operative procedure differed from that of experiments 13 *A* and 13 *B* only in respect to the application of Zenker's solution to both the periosteum and the ends of the costal stumps.

As indicated in one of the roentgenograms (fig. 9 *A*), no new bone was found in the zenkerized periosteal bed, and only a small amount was deposited on the surface of the ends of the rib. The old bone of the ends of these stumps was entirely necrotic.

#### ENDOSTEAL AND OSTEAL OSTEOGENESIS

EXPERIMENT 16 (dog 77).—*Costal regeneration aided by the presence of a segment of rib.*

An entire rib was resected subperiosteally except for a 3 cm. segment which was left undisturbed in the middle of the periosteal bed (diagram 10, fig. 1). The segments which were resected were disarticulated from the vertebra posteriorly and from the costal cartilages anteriorly.

The roentgenogram of the postmortem specimen (fig. 9 *B*), obtained sixty-seven days after operation, shows that the costal regeneration greatly exceeded that obtained in the experiments in which the periosteum was completely decostalized. The limiting effect of the periosteum is strikingly shown.

Viewed microscopically, the new bone presented normal costal architecture with here and there small nodules of cartilage undergoing ossification. The segment of old bone contained both old dead and living bone. The necrotic portions were extensively invaded and were undergoing transformation.

EXPERIMENT 17 (dogs 70 and 76).—*Costal regeneration from costal stumps.*

In each of two dogs a segment of rib 2.5 cm. in length, and with it its periosteum, was resected. Into this space was fitted snugly a segment of costal cartilage which had been removed from the opposite side of the chest. The cartilage not only bridged the gap and made firm contact with the ends of the rib but rested directly on the pleura, the periosteum having been excised (diagram 11, fig. 1).

A portion of the periosteum was used in the control experiment (experiment 9).

The result of the experiment eighty-five days after operation is clearly shown in the roentgenogram (fig. 2 *B*). Extensive proliferation of new bone occurred at the ends of both costal stumps, presenting the picture commonly seen clinically in pseudo-arthritis. Similarly, the flared ends cast shadows of the density of osteosclerosis. However, a narrow bridge of bone can be seen traversing the center of the cartilaginous graft to establish union between the costal stumps.

On gross examination there were a nodular fusiform enlargement at the site of the operation and firm union between the costal segments.

The microscopic appearance of a longitudinal section of this specimen is illustrated in figure 15. The new bone at the ends of the rib was large and unusually dense; it invaded the cartilage irregularly. Through the center of the cartilage there was a continuous core of new bone, and the cartilage appeared to be both old and new. The ends of the rib contained some necrotic old bone.

EXPERIMENT 18.—*Free transplantation of costal segments.*

A. (dogs 77, 78, 17, 80 and 16 G).—*Bone only.*

Eight costal segments from 2 to 3 cm. in length were transplanted to the erector spinae muscles and were recovered at postmortem examinations from sixty-seven to ninety-three days after operation. Some of the grafts which appear in the roentgenograms are illustrated in figures 6 C and 13 B.

All specimens were loosely encapsulated in fibrous tissue and were necrotic in appearance.

Microscopically, five of the transplants appeared to be entirely necrotic, while in the remaining three a few living bone cells near the surface were seen. For a considerable distance from the surface in all specimens the cancellous spaces and haversian canals contained granulation tissue, and the bone in apposition was undergoing absorption. In these areas and along the cortical surfaces there were small excavated indentations, many of which contained giant cells. In all specimens but one there were trabeculae of new bone about the cut ends of the grafts and in the revascularized areas where resorption had taken place. In two, a small amount of new bone had been deposited on the cortical surface, and in no transplant was cartilage seen.

No new bone could be found in one of the two grafts from the old dog (dog 16).

B. (dogs 78 and 80).—*Bone with attached periosteum.*

This experiment differed from the one described in the preceding paragraph in respect to the use of osteoperiosteal grafts. They were removed with strips of periosteum remaining attached to their external surfaces.

Similarly, these transplants appeared to be necrotic and were encapsulated in dense fibrous tissue.

In microscopic section there were definitely more evidence of absorption and larger deposits of new bone, particularly on the cortical surfaces, which presumably were the ones covered with periosteum. Extending out from these surfaces there were areas richly supplied with osteoblasts.

(Cologs 80, 16 G and 17 G). Bone treated with Zenker's solution.

Small segments of seven ribs, some with and some without attached periosteum were soaked for a few seconds in Zenker's solution and immediately buried in the erector spinae muscles.

At the autopsies, from sixty-five to ninety-three days after operation, the segments were removed for microscopic study; all presented the appearance of necrotic bone and encapsulation with fibrous tissue. Some of the grafts are shown in the roentgenogram (fig. 6 D).

In microscopic section the bone of all of the specimens was entirely necrotic, and nowhere was there newly formed bone. The cancellous spaces were extensively invaded by young vascular fibrous tissue, and it appeared that considerable absorption of the old bone had taken place.

#### *Description of Dogs*

Dog	Description	Weight, kg.	Date of Operation	Date of Autopsy	Experiments
19	Large young brown fox	22	5-18-32	8-12-32	15B, 17, 8, 9, 3, 1
21	Large young brown fox	22	5-18-32	8-12-32	11, 15B, 1, 6, 9
31	Large golden pup	29	5-29-32	8-12-32	1, 1, 9
7	Young mongrel collie	19	6-7-32	8-29-32	12, 15A, 15C, 17, 9
27	Large mongrel pup	22	6-9-32	8-15-32	15C, 16, 7, 8, 18A, 9
78	Young mongrel pointer	21.5	6-9-32	8-15-32	5, 8, 18A, 18B, 9
80	Young spitz	18	6-11-32	8-15-32	12, 18A, 1-B, 18C
103	Aged mongrel collie	27	9-15-32	12-18-32	10A, 10B, 10C, 18A, 18C, 9
110	Mongrel pointer pup	18	9-21-32	12-18-32	2, 15A, 18A, 18C, 9
104	Young spaniel mongrel	17	9-22-32	12-18-32	11, 7, 2, 5, 8, 9
84	Mongrel fox terrier pup	11.5	9-10-32	11-12-32	11
82	Young pointer	29	9-12-32	11-16-32	11
81F	Mongrel pup	18.5	9-12-32	11-12-32	13

#### COMMENT

No attempt will be made to review the voluminous literature dealing with the relation of the periosteum to osteogenesis. It is sufficient to note that no truly significant contributions have been made to the early observations and opinions of Duhamel<sup>2</sup> and Ollier<sup>3</sup> that the periosteum has an osteogenic function and to the contradictory experimental results and observations of Macewen<sup>4</sup> expressed in the often quoted words: "While not underestimating the periosteum as a limiting and protecting membrane . . . there are no data to indicate that it can of itself secrete or reproduce bone. It has no osteogenic function."

2. Duhamel du Monceau, H. L.: On the Formation of Bones in Animals and of Wood in Trees, *Rec. périod. d'obs. de méd., de chir. et pharm.* 7:161, 1757.

3. Ollier, M. L.: Artificial Production of Bone by Displacement and Transplantation of Periosteum, *Compt. rend. Acad. d. sc.* 47:905, 1858.

4. Macewen, W.: The Growth of Bone, Glasgow, James Maclehose and Sons, 1912.

These controversial opinions still prevail. While Leriche and Policard,<sup>5</sup> Gallie and Robertson,<sup>6</sup> Cohn and Mann,<sup>7</sup> Murray,<sup>8</sup> Davis,<sup>9</sup> Hunnicut<sup>10</sup> and others have presented important evidence in support of Macewen's views, equally impressive data subscribing to the osteogenic theory of Ollier have been recorded by a large group of investigators, among whom may be mentioned Mayer and Wehner,<sup>11</sup> Axhausen,<sup>12</sup> Lexer,<sup>13</sup> Phemister,<sup>14</sup> Martin,<sup>15</sup> Simon,<sup>16</sup> Rohde,<sup>17</sup> Tomita,<sup>18</sup> Fragenheim,<sup>19</sup> Kropveld,<sup>20</sup> Rollo,<sup>21</sup> Imbert and Jourdan,<sup>22</sup> Polacco,<sup>23</sup>

5. Leriche, R., and Policard, A.: *The Normal and Pathological Physiology of Bone*, translated by Sherwood Moore and J. A. Key, St. Louis, C. V. Mosby Company, 1928.

6. Gallie, W. E., and Robertson, D. E.: *The Repair of Bone*, Brit. J. Surg. 7:211, 1919.

7. Cohn, I., and Mann, G.: *Further Study of Bone Repair*, South. M. J. 9:235, 1916.

8. Murray, C. R.: *The Repair of Fractures*, Minnesota Med. 13:137, 1930.

9. Davis, quoted by Wirtz: *Periosteal Ossification*, Arch. f. orthop. u. Unfall.-Chir. 18:559, 1920-1921.

10. Hunnicut, quoted by Wirtz.<sup>9</sup>

11. Mayer, L., and Wehner, E.: *The Significance of the Individual Components of the Bony Tissue in Regeneration and Transplantation of Bones*, Arch. f. klin. Chir. 103:732, 1914.

12. Axhausen, G.: *The Histological and Clinical Laws of Free Osteoplasia*, Arch. f. klin. Chir. 88:23, 1908.

13. Lexer, E.: *Enderfolge der freien Knochentransplantation*, München, med. Wchnschr. 66:1275, 1919.

14. Phemister, D. B.: *The Fate of Transplanted Bone and the Regenerative Power of Its Various Constituents*, Surg., Gynec. & Obst. 19:303, 1914.

15. Martin, B.: *Bone Regeneration from the Periosteum*, Arch. f. klin. Chir. 120:744, 1922; *Regeneration of Long Bones*, ibid. 113:1, 1919.

16. Simon, R.: *On the Outcome of Bone Grafts and the Conclusions Which Can Be Drawn with Regard to the Choice of Material*, Gaz. med. de Strasbourg 80:404, 1922.

17. Rohde, C.: *The Course of Regenerative Processes in Long Bones*, Arch. f. klin. Chir. 123:530, 1923.

18. Tomita, C.: *Experimental Study of Transplantation of Bone*, Virchows Arch. f. path. Anat. 191:80, 1908.

19. Fragenheim, P.: *Permanent Results of Osteoplasty in the Animal Experiment*, Arch. f. klin. Chir. 93:191, 1910.

20. Kropveld, S. M.: *Experimental Contributions to the Question of Bone Transplantation*, Nederl. maandschr. v. geneesk. 10:684, 1921.

21. Rollo, S.: *Periosteum, Connective Tissue and Calcium Salts in Relation to Osteogenesis*, Rev. di biol. 12:27, 1930.

22. Imbert and Jourdan, R.: *Evolution of Osseous Tissue in Osteo-Periosteal Grafts*, Compt. rend. Soc. de biol. 82:115, 1919.

23. Polacco, E.: *Comparative Research Work on Graftings of Periosteum and of Young Bone*, Arch. per le sc. med. 53:476, 1929.



C (dogs 80, 16 G and 17 G).—*Bone treated with Zenker's solution.*

Small segments of seven ribs, some with and some without attached periosteum were soaked for a few seconds in Zenker's solution and immediately buried in the erector spinae muscles.

At the autopsies, from sixty-five to ninety-three days after operation, the segments were removed for microscopic study; all presented the appearance of necrotic bone and encapsulation with fibrous tissue. Some of the grafts are shown in the roentgenogram (fig. 6 D).

In microscopic section the bone of all of the specimens was entirely necrotic, and nowhere was there newly formed bone. The cancellous spaces were extensively invaded by young vascular fibrous tissue, and it appeared that considerable absorption of the old bone had taken place.

#### *Description of Dogs*

Dog	Description	Weight, Kg.	Date of Operation	Date of Autopsy	Experiments
70	Large young brown female..	22	5/18/32	8/12/32	15B, 17, S, 9, 3, 1
71	Large young brown male....	23.5	5/18/32	8/12/32	11, 15B, 1, 6, 9
72	Large police pup.....	20	5/20/32	8/12/32	4, 1, 9
76	Young mongrel collie.....	19	6/ 7/32	8/29/32	12, 15A, 15C, 17, 9
77	Large mongrel pup.....	21	6/ 9/32	8/15/32	15C, 16, 7, 8, 18A, 9
78	Young mongrel police.....	24.5	6/ 9/32	8/15/32	5, 8, 18A, 18B, 9
80	Young spitz.....	18	6/11/32	8/15/32	12, 18A, 18B, 18C
16G	Aged mongrel collie.....	27	9/15/32	12/18/32	10A, 10B, 10C, 18A, 18C, 9
17G	Mongrel police pup.....	18	9/21/32	12/18/32	2, 15A, 18A, 18C, 9
18G	Young spaniel mongrel.....	17	9/ 2/32	12/18/32	11, 7, 2, 5, 8, 9
81	Mongrel fox terrier pup.....	14.5	9/10/32	11/12/32	14
82	Young police.....	20	9/12/32	11/16/32	14
84F	Mongrel pup.....	18.5	9/12/32	11/12/32	13

#### COMMENT

No attempt will be made to review the voluminous literature dealing with the relation of the periosteum to osteogenesis. It is sufficient to note that no truly significant contributions have been made to the early observations and opinions of Duhamel<sup>2</sup> and Ollier<sup>3</sup> that the periosteum has an osteogenic function and to the contradictory experimental results and observations of Macewen<sup>4</sup> expressed in the often quoted words: "While not underestimating the periosteum as a limiting and protecting membrane . . . there are no data to indicate that it can of itself secrete or reproduce bone. It has no osteogenic function."

2. Duhamel du Monceau, H. L.: On the Formation of Bones in Animals and of Wood in Trees, *Rec. périod. d'obs. de méd., de chir. et pharm.* 7:161, 1757

3. Ollier, M. L.: Artificial Production of Bone by Displacement and Transplantation of Periosteum, *Compt. rend. Acad. d. sc.* 47:905, 1858.

4. Macewen, W.: The Growth of Bone, Glasgow, James Maclehose and Sons, 1912.

These controversial opinions still prevail. While Leriche and Policard,<sup>5</sup> Gallie and Robertson,<sup>6</sup> Cohn and Mann,<sup>7</sup> Murray,<sup>8</sup> Davis,<sup>9</sup> Hunnicut<sup>10</sup> and others have presented important evidence in support of Macewen's views, equally impressive data subscribing to the osteogenic theory of Ollier have been recorded by a large group of investigators, among whom may be mentioned Mayer and Wehner,<sup>11</sup> Axhausen,<sup>12</sup> Lexer,<sup>13</sup> Phemister,<sup>14</sup> Martin,<sup>15</sup> Simon,<sup>16</sup> Rohde,<sup>17</sup> Tomita,<sup>18</sup> Fragenheim,<sup>19</sup> Kropveld,<sup>20</sup> Rollo,<sup>21</sup> Imbert and Jourdan,<sup>22</sup> Polacco,<sup>23</sup>

5. Leriche, R., and Policard, A.: *The Normal and Pathological Physiology of Bone*, translated by Sherwood Moore and J. A. Key, St. Louis, C. V. Mosby Company, 1928.

6. Gallie, W. E., and Robertson, D. E.: *The Repair of Bone*, Brit. J. Surg. 7:211, 1919.

7. Cohn, I., and Mann, G.: *Further Study of Bone Repair*, South. M. J. 9:235, 1916.

8. Murray, C. R.: *The Repair of Fractures*, Minnesota Med. 13:137, 1920.

9. Davis, quoted by Wirtz: *Periosteal Ossification*, Arch. f. orthop. u. Unfall-Chir. 18:559, 1920-1921.

10. Hunnicut, quoted by Wirtz.<sup>9</sup>

11. Mayer, L., and Wehner, E.: *The Significance of the Individual Components of the Bony Tissue in Regeneration and Transplantation of Bones*, Arch. f. klin. Chir. 103:732, 1914.

12. Axhausen, G.: *The Histological and Clinical Laws of Free Osteoplasia*, Arch. f. klin. Chir. 88:23, 1908.

13. Lexer, E.: *Enderfolge der freien Knochen transplantation*, München. med. Wchnschr. 66:1275, 1919.

14. Phemister, D. B.: *The Fate of Transplanted Bone and the Regenerative Power of Its Various Constituents*, Surg., Gynec. & Obst. 19:303, 1914.

15. Martin, B.: *Bone Regeneration from the Periosteum*, Arch. f. klin. Chir. 120:744, 1922; *Regeneration of Long Bones*, ibid. 113:1, 1919.

16. Simon, R.: *On the Outcome of Bone Grafts and the Conclusions Which Can Be Drawn with Regard to the Choice of Material*, Gaz. med. de Strasbourg 80:404, 1922.

17. Rohde, C.: *The Course of Regenerative Processes in Long Bones*, Arch. f. klin. Chir. 123:530, 1923.

18. Tomita, C.: *Experimental Study of Transplantation of Bone*, Virchows Arch. f. path. Anat. 191:80, 1908.

19. Fragenheim, P.: *Permanent Results of Osteoplasty in the Animal Experiment*, Arch. f. klin. Chir. 93:191, 1910.

20. Kropveld, S. M.: *Experimental Contributions to the Question of Bone Transplantation*, Nederl. maandschr. v. geneesk. 10:684, 1921.

21. Rollo, S.: *Periosteum, Connective Tissue and Calcium Salts in Relation to Osteogenesis*, Rev. di biol. 12:27, 1930.

22. Imbert and Jourdan, R.: *Evolution of Osseous Tissue in Ostco-Periosteal Grafts*, Compt. rend. Soc. de biol. 82:115, 1919.

23. Polacco, E.: *Comparative Research Work on Graftings of Periosteum and of Young Bone*, Arch. per le sc. med. 53:476, 1929.

Schepelmann,<sup>24</sup> Tricini,<sup>25</sup> Nakahara and Dilger,<sup>26</sup> Jokoi,<sup>27</sup> Berthier,<sup>28</sup> Baschkirzen,<sup>29</sup> Hintzsche,<sup>30</sup> Petrow,<sup>31</sup> Lazzarini,<sup>32</sup> Riess,<sup>33</sup> Vogel,<sup>34</sup> Willich,<sup>35</sup> Partsch,<sup>36</sup> Seifert,<sup>37</sup> Hass,<sup>38</sup> Blaisdell,<sup>39</sup> Blaisdell and Cowan,<sup>40</sup> Berg and Thalheimer,<sup>41</sup> Mock,<sup>42</sup> Ham<sup>43</sup> and Haldeman.<sup>44</sup>

24. Schepelmann, E.: Free Transplantation of Periosteum, *Arch. f. klin. Chir.* **101**:499, 1913.

25. Tricini, W.: Experimental Contributions to the Study of Periosteal Transplantation, *Ztschr. f. orthop. Chir.* **30**:69, 1912.

26. Nakahara, T., and Dilger, A.: Subcutaneous and Intramuscular New Formation of Bone by Injection or Implantation of Periosteal Emulsions, *Beitr. z. klin. Chir.* **63**:235, 1909.

27. Jokoi, T.: Experimental Contribution to the New Formation of Bone by Means of Injection or Implantation of Periosteal Emulsions, *Deutsche Ztschr. f. Chir.* **18**:433, 1912.

28. Berthier, A.: Histological and Experimental Studies on Muscular Osteoma, *Arch. de méd. exper. et d'anat. path.* **4**:601, 1894.

29. Baschkirzen, N. J., and Petrow, N. M.: Contributions on Free Bone Transplantations, *Deutsche Ztschr. f. Chir.* **113**:490, 1912.

30. Hintzsche, E.: The Osteoblast Theory and the Modern Views of the Normal Process of Ossification, *Ztschr. f. d. ges. Anat.* **27**:413, 1927.

31. Petrow, N. M.: The Source of Regeneration in Bone Transplantation, *Arch. f. klin. Chir.* **105**:915, 1914.

32. Lazzarini, L.: Different Reaction of Periosteum and Connective Tissue of the Host to Grafts of Bone, *Arch. di ortop.* **43**:65, 1927.

33. Riess, E.: Experimental Studies on the Bone Forming Power of the Periosteum, *Arch. f. klin. Chir.* **129**:750, 1924.

34. Vogel, K.: The Question of Osteoplastic Activity of the Periosteum, *Zentralbl. f. Chir.* **43**:794, 1916.

35. Willich, C. T.: Experiments in Bone Regeneration and Formation of Pseudoarthroses, *Arch. f. klin. Chir.* **129**:203, 1924.

36. Partsch, F.: Studies of Bone Regeneration, *Deutsche Ztschr. f. Chir.* **187**:145, 1924.

37. Seifert, E.: Periosteum and Endosteum in Osteogenesis, *Arch. f. Orthop.* **17**:329, 1920.

38. Hass, S. L.: Regeneration of Bone from Periosteum, *Surg., Gynec. & Obst.* **17**:164, 1913.

39. Blaisdell, F. E.: The Osteogenic Function of the Periosteum, *Arch. Surg.* **11**:933 (Dec.) 1925.

40. Blaisdell, F. E., and Cowan, J. F.: Healing of Simple Fractures, *Arch. Surg.* **12**:619 (March) 1926.

41. Berg, A. A., and Thalheimer, W.: Regeneration of Bone, *Ann. Surg.* **67**:331 (March) 1918.

42. Mock, H. E.: Periosteal Transplants in Repair of Delayed Union, *Surg., Gynec. & Obst.* **46**:641, 1928.

43. Ham, A. W.: A Histological Study of the Early Phases of Bone Repair, *J. Bone & Joint Surg.* **12**:827, 1930.

44. Haldeman, K. O.: The Role of the Periosteum in the Healing of Fractures: Experimental Study, *Arch. Surg.* **24**:440 (March) 1932.

## CONCLUSIONS

1. The costal periosteum is directly or indirectly osteogenic. In young dogs, new bone was constantly deposited on the cambium surface of the periosteum, but in no instance was bone laid down on the dechondralized surface of the perichondrium. Although both membranes, the periosteum and the perichondrium, are composed of fibrous tissue, the periosteum has the important additional inner, richly cellular layer which has been designated by the terms cambium (Billroth<sup>44</sup>), osteogenic (Ollier<sup>45</sup>), proliferative (Virchow<sup>46</sup>) and osteoblastic (Stretzloff<sup>45</sup>). Stripped of this layer of cells (experiment 12), the periosteum apparently was deprived of its osteogenic function and was no more conducive to the formation of new bone than was the dechondralized perichondrium. Nakahara and Dilger<sup>26</sup> succeeded experimentally in obtaining proliferation of new bone from transplanted emulsions of scrapings of the periosteum; these emulsions presumably were composed principally of cells of the cambium layer.

Gallie and Robertson<sup>6</sup> have presented experiments indicating that costal regeneration results entirely from proliferation from the costal stumps. They obtained no regeneration in experiments in which these stumps were tightly sealed from the periosteal beds. Similar experiments carried out by Mayer and Wehner<sup>11</sup> and me yielded results which were absolutely contradictory, as were the results of my experiments in which complete reformation of the ribs took place in the totally decostalized periosteal beds where there were no costal stumps from which proliferation could take place. To exclude the cartilaginous stumps as a possible source for the new bone, both the rib and its cartilage were totally extirpated, and, as shown in experiment 2, complete reformation of the ribs occurred.

Always there exists the probability, as Martin<sup>15</sup> has definitely pointed out, that microscopic fragments of bone remained attached to the periosteum and that these fragments gave rise to the newly formed bone. Obviously a conclusive investigation of this problem is impossible. However, the negative findings in thirteen of the fourteen fresh strips of periosteum which were studied in experiment 9 are at least indicative that residual fragments are not present in large quantities. It is also significant that in the experiments in which periosteum was transplanted and in those in which ribs regenerated in periosteal beds, no old bone or evidence of residual fragments was found. It is unlikely that absorption of old bone would have been so complete that no vestige remained.

---

45. Quoted by Riess.<sup>33</sup>

The author has shown in a previous publication <sup>46</sup> that large fragments of a rib, when transplanted into a dechondralized perichondrial bed, establish union with each other and with the sternum and rib, thereby forming a continuous piece of bone with typical costal architecture. The new bone, however, appeared to arise entirely within and from the transplants, and the perichondrium provided merely a protective vascular membrane which aided proliferation. The analogy might be applied to the decostalized periosteum and the possible adherent fragments of bone. This deduction, however, seems inapplicable when one compares the quantitative osteogenic response in the two groups of experiments. The decostalized periosteum containing at most microscopically minute fragments of bone gave rise to an infinitely more rapid and luxuriant growth of new bone than did the large costal grafts in the perichondrial bed.

2. Costal regeneration is limited by the periosteum and fails in the absence of the periosteum. When this membrane was removed from the space between the costal stumps, the newly formed bone merely sealed the open cancellous spaces at the ends of the rib and did not proliferate beyond the cut edge of the periosteum.

Sauerbruch <sup>47</sup> has reported contradictory clinical observations. He cited the case of a patient in whom costal regeneration took place after both the ribs and the periosteum had been removed.

In experiment 17, new bone did proliferate beyond the limits of the periosteum, but the proliferation traversed the center of a transplanted segment of cartilage. It is possible that the cartilage, besides providing an ossifiable medium, maintained a space between the ends of the rib into which new bone could proliferate without interference from scar tissue.

It is interesting that for a short distance the ends of the costal stumps in each experiment became necrotic except for surviving cells along the surfaces and at the borders of vascular spaces.

For some reason which is not apparent, much more new bone was deposited in each instance about the end of the anterior than about the end of the posterior stump.

3. Reparative osteogenesis is influenced by various factors. Age normally exerts an influence which is physiologic. It is a well established fact that the younger the subject, man or animal, the more active are all of the reparative processes of the body tissues. This is particularly true of reparative osteogenesis and has been stressed by the clinical and experimental observations of Ollier,<sup>3</sup> Martin,<sup>12</sup> Lexer,<sup>13</sup>

46. Bísgard, J. D.: *Experimental Studies of Reparative Costal Chondrogenesis and of Transplanted Bone*, Surg., Gynec. & Obst. 58:817 (May) 1934.

47. Sauerbruch, F.: *Tr. Surg. Cong., Berlin, 1921*; quoted by Martin.<sup>12</sup>

Axhausen,<sup>12</sup> Riess<sup>33</sup> and many others. Riess found that new bone was deposited in all periosteal transplants in dogs less than 9 months of age, and no new bone was found in transplants in older animals. The influence of age is shown strikingly in the comparison of experiment 10 and the accompanying illustration (fig. 12) with the similar experiments and illustrations for the younger dogs.

The influence of the blood supply as a factor in osteogenesis is also well recognized but not thoroughly appreciated. In the rich blood supply of the periosteum Simon,<sup>16</sup> Seiffert<sup>37</sup> and others found the principal source of its osteogenic function. As a result of the interruption of much of its blood supply, the periosteum in experiment 11 gave rise to no new bone. The author has observed the exact clinical counterpart in thoracic operations which necessitated the ligation of several pairs of intercostal blood vessels.

Experiments 13 and 14 indicated that the deposition of new bone by the periosteum is prevented by firm and intimate contact with muscle or with a foreign body such as a rubber bag. I had the opportunity to observe the same result in a patient with pulmonary tuberculosis in whom a rubber bag had been used in an extrapleural pneumolysis to compress the lung and the extrapleural tissues, the latter including the periosteum. Contradictory experimental results, however, were obtained by Oughterson and Harvey.<sup>48</sup> In their animals, costal regeneration took place in the periosteal beds despite the contact of rubber bags. The newly formed ribs are clearly shown in their illustrative roentgenograms. In their experiments the bags were filled with air; when recovered at autopsy they were much smaller, as a result of deflation. They also found it unnecessary to aspirate fluid from the wounds. This discrepancy in experimental results shows the far-reaching influence on osteogenesis of small variations in experimental procedure. It is probable that in my experiments the periosteum was constantly subjected to firmer contact with the foreign body. Trauma which probably removed no more than the cambium layer was sufficient to prevent reparative osteogenesis in experiment 12.

Thermal cauterization and chemical electrical coagulation may either merely retard or entirely prevent reparative osteogenesis, depending on the extent and the degree of destruction produced by these agents. Goeldel<sup>49</sup> and Klapp<sup>50</sup> reported in 1921 that no costal regenera-

48. Oughterson, A. W., and Harvey, S. C.: Localized Collapse of the Lung by Means of an Extrapleural Balloon, *Yale J. Biol. & Med.* 3:139 (Dec.) 1930.

49. Goeldel, V.: Ueber Versuche die Knochenregenerationsfähigkeit des Rippenperiostes nach Rippenresektion zu verhüten, *Inaug. Dissert.*, Berlin, 1911.

50. Klapp, R.: Dekompression Operationen am Thorax, *Verhandl. d. deutsche Gesellsch. f. Chir.* 40:202, 1911.

tion took place from periosteum which had been seared with the thermal cautery. Klapp also prevented regeneration by the application of nitric acid. Bircher and Kuettner<sup>51</sup> used phenol. Meiss<sup>52</sup> obtained the same result with less destructive chemical solutions. He used zinc chloride and a dilute solution of formaldehyde U.S.P. (1:10) in some experiments, chromic acid in others and Zenker's solution in still others. Head<sup>53</sup> obtained the same results from the use of chromic acid and Zenker's solution and added silver nitrate to the list. Torroca<sup>54</sup> prevented regeneration in the animals in which he used the thermocautery, phenol, a dilute solution of formaldehyde U.S.P. (1:10) and Baum's liquid. The application of pure silver nitrate and of alcohol retarded but did not prevent the formation of new bone. Van Allen<sup>55</sup> has reported that the application of a dilute solution of formaldehyde U.S.P. (1:10) in a series of cases delayed but did not prevent costal regeneration.

In my experiments, no new bone was found in the periosteal beds which had been treated thoroughly with Zenker's solution. Regeneration progressed normally from the periosteum when only the ends of the rib were zenkerized, but there was definite retardation of absorption of old bone and of proliferation of new bone at the ends of the costal stumps. Transplanted zenkerized costal segments had the appearance of encapsulated foreign bodies. They were entirely necrotic and formed no new bone but were considerably invaded by granulation tissue. In contrast, the untreated transplants, also necrotic, were extensively invaded by granulation tissue, were rapidly undergoing absorption and had given rise to some new bone. Much more new bone was present in the grafts covered with periosteum and on the cortical surfaces, which presumably had a covering of periosteum.

---

51. Bircher and Kuettner, quoted by Torroca.

52. Meiss, W. C.: *Experimenteller Beitrag zur Vereinfachung der Thorakoplastik in mehreren Timpf, Zentralbl. f. Chir.* 6:349, 1930.

53. Head, J. R.: *Prevention of the Regeneration of the Ribs, Arch. Surg.* 14:1209 (June) 1927.

54. Torroca, L.: *Ricerche sperimentali sui mezzi atti ad impedire la rigenerazione ossea dopo l'asportazione sottoperiosteale delle costole, Clin. chir.* 6:1433, 1930.

55. Van Allen, C. M.: *Chemical Treatment of the Periosteum, Ann. Surg.* 97:368 (March) 1933.

# FABELLA (SESAMOID IN THE LATERAL HEAD OF THE GASTROCNEMIUS)

CHARLES J. SUTRO, M.D.\*

MAURICE M. POMERANZ, M.D.

AND

SYDNEY M. SIMON, M.D.

NEW YORK

The sesamoid bone known as the fabella—which literally means “little bean”—is found inconstantly in man on the anterior gliding surface of the external head of the gastrocnemius muscle. Rarely, a sesamoid is seen on the medial head of the gastrocnemius muscle. The inconstancy of the fabella in man and of its location about the knee joint, as evidenced by roentgenographic examination, may be misleading in the diagnosis of conditions of the knee joint (fig. 1 *A*). In rats, cats, rabbits and other animals sesamoids are constantly present<sup>1a</sup> both in the lateral and in the medial heads of the gastrocnemius muscles (figs. 2 *A*, and 3). In these animals one or two additional ossicles are present on the popliteus muscle facing the posterior surface of the tibia.

Sesamoids—for example, those on the lateral or medial heads of the gastrocnemius muscles—are each derived from a specific anlage. The fabellae are not dependent on the activity of the knee joint for their occurrence. Gruber<sup>1b</sup> found that fabellae first appeared as cartilaginous islands at the age of 10. At 17 years of age a center of ossification was apparent in the cartilaginous sesamoid. The fabella, except at the site for the articular cartilage, is attached by Sharpley's fibers to the tendon of the gastrocnemius muscle and to the posterior ligament of the knee joint. The sesamoid is cancellous in structure.

The fabellae, usually bilateral, are located from one-half to one and a half inches (1.27 to 3.77 cm.) above the proximal tip of the fibula when the knee is flexed at an angle of from 150 to 160 degrees. Occasionally the sesamoid can be visualized roentgenographically at the level of the knee joint. Their location may be lateral, posterior or medial to the external femoral condyle. Normally, the ossicles on the lateral head of the gastrocnemius muscle appear to be in close proximity to the posterior surface of the external femoral condyle. As there is a

---

\* Brown Orthopedic Research Fellow.

From the Departments of Roentgenology and Pathology, Hospital for Joint Diseases.

1. (a) Pfitzner, W.: Beiträge zur Kenntnis des menschlichen Extremitätenskeletts, *Morphol. Arb.* 1:517, 1891. (b) Gruber, quoted by Pfitzner.



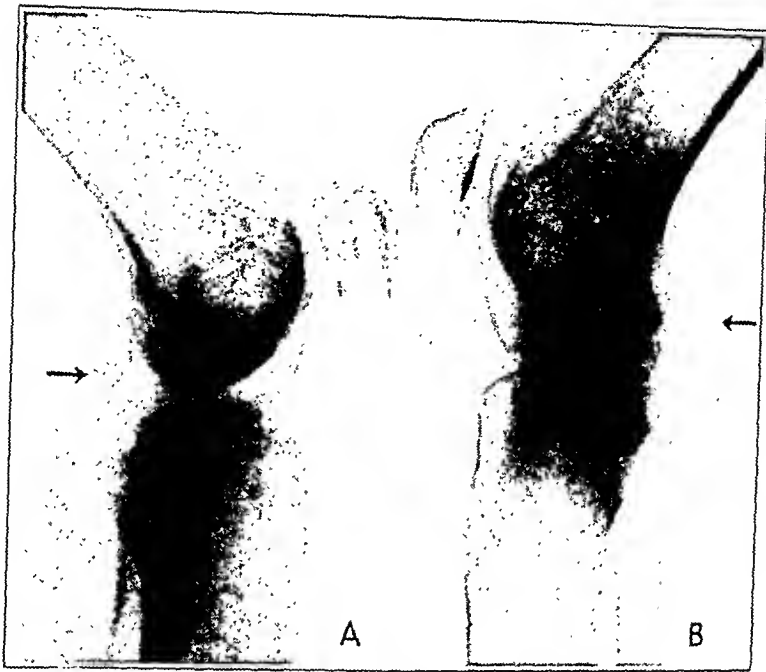


Fig. 1.—*A*, roentgenogram of the left knee. Note the normal position of the sesamoid. *B*, roentgenogram of the right knee (synovitis with effusion). Note the backward displacement of the fabella.

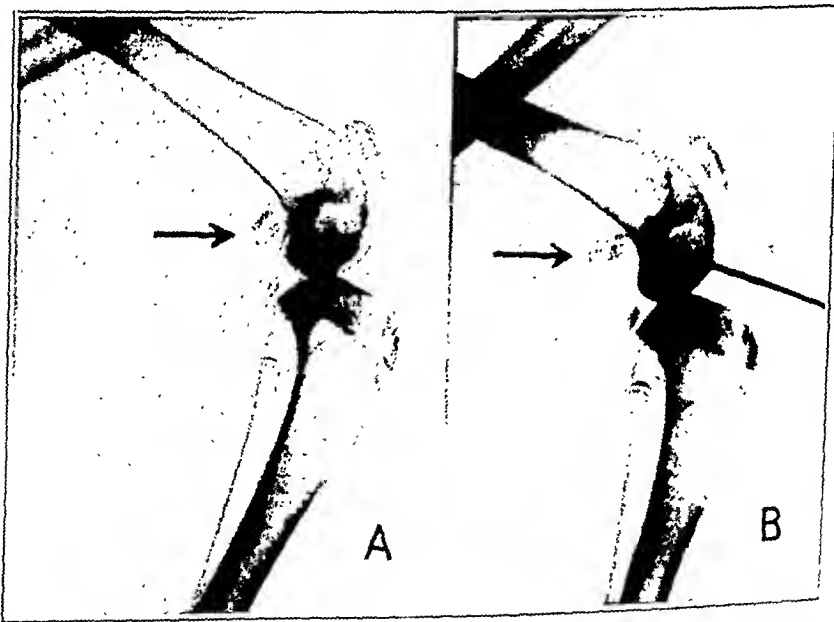


Fig. 2.—Roentgenograms of a rabbit's knee. In *A*, note the double femoral and the single tibial sesamoids. *B*, note the posterior and upward displacement of the femoral sesamoids after an intra-articular injection of saline solution.



Fig. 3.—Photomicrograph of a vertical section through the knee joint of a young rat: (a) fabella; (b) femoral condyle; (c) semilunar cartilage containing normal bone; (d) tibia.



Fig. 4.—A, roentgenogram of the right knee. Note the presence of a medial and lateral sesamoid. B, roentgenogram of the right knee (osteo-arthritis). Note the irregular appearance of the fabella.

normal area of rarefaction in the external femoral condyle, the sesamoids are often seen by roentgen examination in the anteroposterior view. These ossicles vary in diameter from several millimeters to 2 cm. In roentgenographic pictures they appear usually semilunar in the lateral view and either elliptic or circular in the anteroposterior projection. Many variations in shape, however, exist.

#### ROENTGENOGRAPHIC OBSERVATIONS

In this study, 806 roentgenograms of the knee joints of 700 patients were examined. First, we wanted to determine the incidence of fabellae in this number of patients, each of whom had symptoms referable to one or both knee joints. Second, we desired to study variations in the appearance of the ossicles. Third, we sought to ascertain whether their

#### *Summary of Data on Which Study Was Based*

Age, Years	Patients Without Fabellae	Patients with at Least a Single Fabella	Patients Examined	Incidence (by Roentgenographic Examination) of at Least a Single Fabella, per Cent
1 to 10.....	71	0	71	0
11 to 20*.....	99	2	92	2
21 to 30.....	89	13	102	12
31 to 40.....	108	15	123	12
41 to 50.....	128	19	147	12.9
51 to 60.....	95	22	117	18.8
61 to 70†.....	30	9	39	23
71 to 80.....	7	1	8	12.5
81 to 90.....	1	0	1	0
Total.....	619	81	700	11.5

\* A fabella was seen roentgenographically in a boy 12 years of age.

† The higher incidence of fabellae in the older groups can be attributed possibly to calcification or ossification of previously existing sesamoids that originally were not sufficiently calcified to be visualized roentgenographically.

presence was of any aid in the diagnosis of lesions in or about the knee joint.<sup>2</sup>

Only 106 patients had had roentgenograms taken of both the right and the left knee. Nineteen of these patients had fabellae. Sixteen had bilateral fabellae (one ossicle in the external head of the right and the other in that of the left gastrocnemius muscle). Two others had only one sesamoid (one patient having it in the lateral head of the right and the other in that of the left gastrocnemius muscle). One had sesamoids in the lateral and medial heads of the right gastrocnemius muscle (fig. 4 A). In these 106 patients the incidence of bilateral fabellae (a sesamoid in the external head of the right and one in that of the left gastrocnemius muscle) was about 15 per cent.

In 318 cases the right knee alone was roentgenographed (in the usual projections), and single sesamoids were present in 36 cases (about 11 per cent). The roentgenographic examination of the left

2. In these studies Dr. H. L. Jaffe gave helpful criticism.

knees of 276 additional patients showed an ossicle in the lateral head of the gastrocnemius muscle in 26 instances (about 9.5 per cent). Thus, in our group of 700 patients, 345 of whom were males and 355, females, the incidence by roentgenographic examination of at least a single fabella was 11.5 per cent for each sex.

The accompanying table gives the age grouping of the patients and the percental incidence in each group of at least a single fabella.

In 193 patients there was osteo-arthritis of the knee. Thirty-eight of these had at least a unilateral fabella (19 per cent). In 7 of these 38 patients, irregularities in the sesamoids suggesting arthritis were noted (fig. 4 B). Among 9 cases of synovitis of the knee of unknown origin in which fabellae were seen, there was abnormal displacement of the fabella in 4 cases (fig. 1 B). An irregular large fabella was noted in the roentgenogram of the knee of a patient suffering from gout. The ossicle appeared to be involved in the disease process, as were the bones comprising the knee joint. In 2 cases of Paget's disease, the lateral sesamoid appeared within normal limits.

#### COMMENT

In the literature the incidence of the fabella has been reported as varying from 10 to 20 per cent. The higher figures were based on anatomic studies and the lower ones on roentgenologic investigations.<sup>3</sup> Fabellae seem to take part in pathologic processes. Some seem to become arthritic; some become involved in general metabolic disorders, as gout; some can be fractured,<sup>4</sup> while others become involved in what is described as osteochondritis.<sup>5</sup> A rare lesion is the pinching of the fabella in the knee joint, which is possibly due to a herniation of the posterior capsule.<sup>6</sup>

3. Pancoast, H. K.: Radiographic Statistics of the Sesamoid in the Tendon of the Gastrocnemius, Univ. Pennsylvania M. Bull. 22:213, 1909. Skinner, E. H.: Loose Body Versus Sesamoid Bone in the Outer Head of the Gastrocnemius, New York State M. J. 90:153, 1909. Fischer, H.: Beitrag zur Kenntnis der Skelett-varietäten, Fortschr. a. d. Geb. d. Röntgenstrahlen 19:43 (July) 1912. Ulrichs, B.: Fabella, Zentralbl. f. Chir. 53:1369 (May 29) 1926. Simon, H.: Fabella, ibid. 53:650 (March 13) 1926. Sonntag, E.: Zur Frage der Fabella, ibid. 54:660 (March 12) 1927. Vogel, K.: Ein Fall von doppelter Fabella, ibid. 54:2566 (Oct.) 1927. Pick, H.: Zur Frage der Fabella, ibid. 54:1743 (July 9) 1927. Grassmuck, J.: Ueber das Vorkommen der Fabella, ibid. 55:1031 (April 28) 1928. Gregory, A.: Ossiculum sesamoideum verum muscoli gastrocnemii externi (Gruber), ibid. 55:2518 (Oct.) 1928. Yano, K.: Das Os sesamoideum muscoli gastrocnemii lateralis bei den Japanern, Folia anat. japon. 6:241 (May) 1928. Kremser, K.: Beobachtung einer Fabella im lateralen und medialen Gastrocnemiuskopf, Röntgenpraxis 2:134 (Feb.) 1930.

4. Sagel, J.: Fracture of Two Femoral Sesamoid Bones, Am. J. Surg. 18:507 (Dec.) 1932.

5. Lepoutre, C.: Sésamoïde douloureux (sésamoïde du jumeau externe). Guérison par l'extirpation, Rev. d'orthop. 16:234 (May) 1929.

6. Heydemann, H.: Die Fabella, Röntgenpraxis 1:950 (Dec.) 1929.

Commonly we see the coexistence of fabellae with intra-articular bodies. The sesamoids are usually differentiated by their bilateral symmetry in size, shape and location. Reports have been cited in which it was stated that fabellae considered as intra-articular bodies were surgically removed.<sup>7</sup> An important method for the differentiation of intra-articular and extra-articular bodies is that of roentgenographic examination of the knee joint after sufficient amounts of opaque material, saline solution or air have been injected.<sup>8</sup> In figure 2 *B*, the fabellae of the rabbit are seen displaced backward and upward by the injected fluid. A similar condition is presented clinically in figure 1 *B*, in which the ossicle is seen displaced posteriorly by the effusion. In addition, displacement of the sesamoid should be an important sign in the detection and location of tumors or cysts of the soft tissues about the posterior portion of the knee joint. Thus, a swelling originating intra-articularly may, if large enough, displace the fabellae posteriorly. A mass in the gastrocnemius muscle or in the posterior capsule, however, may force the fabellae toward the knee joint. The sesamoid of the gastrocnemius muscle must, in addition, be differentiated from chip fractures, paracondylar and meniscal calcifications or ossifications, calcified glands and calcified blood vessels.

#### SUMMARY AND CONCLUSIONS

(a) A study of roentgenograms of the knee joints of 700 patients revealed the presence of at least a single fabella in 11.5 per cent.

(b) The sesamoids seem able to undergo pathologic alterations such as arthritis, fracture or osteochondritis.

(c) The fabella may be a bony landmark (as evidenced by roentgenographic examination) for the recognition of effusions into the knee joint and for the differentiation of swellings or masses near the posterior ligament of the knee joint.

---

7. Wolff, H.: Ueber die praktisch chirurgische Bedeutung des Sesambeines im Musculus gastrocnemius, *Berl. klin. Wchnschr.* **41**:1052, 1904. Flecker, H.: Roentgenographic Observations of the Time of Appearance of Epiphyses and Their Fusion with the Diaphyses, *J. Anat.* **67**:118 (Oct.) 1932.

8. Oberholzer, J.: Die Arthro-Pneumoradiographie, *Beitr. z. klin. Chir.* **158**: 113, 1933.

# EPILEPSY SECONDARY TO HEAD INJURY

MARK ALBERT GLASER, M.D.

AND

FREDERICK P. SHAFER, M.D.

LOS ANGELES

That trauma to the head may produce epileptic seizures is a well known fact, but to ascertain in a given case of generalized epilepsy whether the epilepsy may reasonably be considered due to a previous head injury or whether it is of a nontraumatic type is not always easy. The following report of a case exemplifies such a problem:

A Negro man, aged 36, an electrician's helper, reported for examination with the complaint of generalized convulsions. Fourteen months previous to entrance, the head of a hammer flew from the handle while he was driving a nail and struck him in the right parietal region of the skull. He suffered an abrasion of the scalp, but there was no deep laceration, and sutures were unnecessary. Roentgenograms did not reveal a fracture. The patient was dazed, but there was considerable doubt as to whether he was unconscious at the time of the injury; if he was unconscious, it was only momentarily. He returned to his duties the next morning and continued to work for a period of sixteen months. He was then discharged on account of economic conditions. On his discharge he applied for compensation, stating that convulsions had developed three months after the injury, which he believed were a result of the trauma. His story was doubted and a detective investigation carried out. The investigator was able to establish the occurrence of the first convulsion as being five weeks after the injury; he could not find any evidence of convulsions prior to the injury. Examination by us fourteen months after the injury revealed definite proof of generalized seizures which were preceded by an aura which consisted of a peculiar abdominal sensation extending upward to the head; this was preceded by a cry and followed by generalized tonic contractions; the contractions, in turn, were succeeded by clonic spasms. There was loss of sphincter control involving both the rectum and the bladder. The patient then remained unconscious for a period varying from one-half hour to several hours, and it was several days before he returned to normal. During the examination it was evident that this man was untruthful but exceedingly shrewd, evasive and unreliable. Physical and neurologic examinations, as well as laboratory tests, revealed no abnormalities.

The case was settled for the sum of \$1,700.

At a reexamination by us thirty months after the injury the patient reported a marked increase in the severity and frequency of the convulsion, intense headaches and fatigue so marked that he was totally incapacitated. Examination indicated evasiveness to questions and definite attempts to mislead the examiner. Again neurologic and physical examinations revealed no abnormalities. A ruling of the Industrial Accident Commission did not permit a reopening of the case in view of the fact that a compromise settlement and release had been made.

---

Presented before the Neurological Section at the Sixty-Second Annual Session of the California Medical Association, Del Monte, April 27, 1933.

Four questions of importance confront one in the study of generalized traumatic epilepsy, the solution of which we shall consider in this paper, which is based on a review of our series of cases of head injury, as well as on a study of the literature:

1. Did the head injury cause the epilepsy?
2. Following a head injury, how far may one go in prognosticating the probability that epilepsy will or will not develop as a result of the injury?
3. Is there any method of preventing the occurrence of this sequela?
4. Is there any method of therapy to be advised for traumatic generalized epilepsy?

#### CLASSIFICATION OF EPILEPSY

Epilepsy secondary to trauma may be divided into four types: (1) focal epilepsy; (2) generalized epileptic states, including both grand mal and petit mal; (3) so-called "hystero-epilepsy," and (4) reflex epilepsy. The differentiation is not always absolute, and in a case in which the condition primarily belongs to one of these groups there may be occasional seizures similar to those of one of the other groups.

A question rarely arises with regard to the etiologic rôle of the preceding trauma in any of these types, except in cases in which the convulsions are generalized. Our study is therefore concerned chiefly with this form. We shall, however, in a cursory manner consider the other three types.

*Focal.*—Focal, or jacksonian, epilepsy is a type which involves purely or primarily a certain localized area of the body, perhaps spreading from this to include the entire organism. It has been established by the work of numerous investigators that head trauma may produce pathologic changes in the brain in cases in which there are no neurologic signs as well as in those which present abnormal objective findings.

When a patient has a convulsive seizure of this form, it is important to study the seizure carefully as to both objective and subjective elements. By so doing the seizure may be classified into a focal group, and therapeutic measures may be directed toward a definite part of the brain. Hughlings Jackson first described the motor type, and for this reason the motor attack has been termed jacksonian epilepsy. Foerster<sup>1</sup> has verified the type of seizure and its point of origin by electrical stimulation of the cortex in conscious patients. This work has also been carried out by Penfield.<sup>2</sup> With this concept in view, Penfield and

1. Foerster, O.: Die Pathogenese des epileptischen Krampfanfalles, *Deutsche Ztschr. f. Nervenhe.* **94**:15, 1926.

2. Penfield, W.: The Mechanism of Cicatricial Contraction in the Brain, *Brain* **50**:499, 1927.

Gage<sup>3</sup> have placed under the headings of epileptic seizures, or fits, the following manifestations: (1) clonic and tonic spasm; (2) paresthesias of the limbs or of the body; (3) hallucinations of sight, sound, smell and taste; (4) certain disturbances of consciousness and dream states; (5) visceral sensations (epigastric and thoracic), and (6) autonomic phenomena (such as disturbances of respiration, heart beat, secretion of tears, perspiration and flushing).

Deviation of the head and eyes to the side opposite the hemisphere involved is a valuable lateralizing sign. Seizures due to involvement of the frontal lobe are characterized by a loss of consciousness, followed by a turning of the eyes, head and body to the opposite side and by a simultaneous convulsion of the opposite lower extremity. In cases of involvement of the precentral gyrus, consciousness is usually lost late, and a tingling sensation may follow the jacksonian attack. In general, turning without aura points to a localization in front of the precentral convolution and turning with aura points to an area behind it. Involvement of the precentral convolution results in local clonic spasms with late loss of consciousness. Seizures arising in the postcentral convolution consists of numbness, tingling or a loss of sensation. Seizures beginning in the occipital lobe often have as their first phenomenon an optical aura such as flame, stars, light, etc., generally in the opposite visual field. Involvement of the temporal lobe may produce buzzing sounds and dizziness, as well as dreamy states, and if the uncinate gyrus is involved, the occurrence of peculiar odors.

In one article Foerster and Penfield<sup>4</sup> described a series of twelve clinical cases in which they demonstrated remarkable verification, on surgical tests, of the theoretical areas of localization and confirmed the origin of attacks in this type of epilepsy.

An epileptic attack is fundamentally an active process of stimulation and not a release phenomenon. The cicatrix, after injury to the brain or meninges, is primarily a network of fibrous astrocytes which, as time passes, becomes vascularized, with replacement of nerve cells and fibers by connective tissue. The time of onset of the convulsions after injury in 12 cases was from five months to fourteen years, at which time the vascular plexus of the involved area is well developed while the nerve fibers are much diminished. It appears, accordingly, that the initiation of the seizures is associated with the vascular condition rather

3. Penfield, W., and Gage, L.: Cerebral Localization of Epileptic Manifestations, *Arch. Neurol. & Psychiat.* 30:728 (Oct.) 1933.

4. Foerster, O., and Penfield, W.: Der Narbenzug am und im Gehirn bei traumatischer Epilepsie in seiner Bedeutung für das Zustandekommen der Anfälle und für die therapeutische Bekämpfung derselben, *Ztschr. f. d. ges. Neurol. u. Psychiat.* 125:475, 1930.



than with the nervous elements and that the scar must involve traction on the blood vessels. Foerster and Penfield suggested the hypothesis that a vasomotor reflex, secondary to this traction, is responsible for the initiation of convulsive seizures.

Penfield<sup>2</sup> and Foerster<sup>5</sup> have demonstrated as regards man, and Wortis,<sup>6</sup> as regards animals that after an injury to the brain, if the damaged tissue is not removed, a scar rapidly forms composed of connective tissue and fibrous astrocytes with a marked vascular plexus. The scar becomes adherent to the meninges on the one hand and to the brain on the other. As time advances, it constantly contracts, causing a pull on the cerebral tissue. As this process continues, enlargement of one or both ventricles with internal hydrocephalus often develops, and frequently both ventricles become displaced to the side of the lesion, thus causing the so-called "wandering ventricles."

Foerster and Penfield<sup>7</sup> have pointed out the value of encephalography and also have made the following surgical recommendations: In cases of traumatic epilepsy all the involved tissue of the dura mater and of the brain should be excised. The excision must be extensive enough to remove any scar tissue and all the altered tissue. If the ventricle has been enlarged or displaced toward the side of the lesion so as to have reached almost to the surface, it must be incised and widely opened. Foerster and Penfield have experimentally demonstrated that a smooth excision of brain tissue does not cause new scar tissue to form. They repair the dura mater by plastic surgery with the use of fascia lata and leave the orifice in the bone of the skull open. Glaser, Thienes and Beerman (an article is to be published later) have demonstrated experimentally on animals that animal membrane is just as efficient as fascia lata.

Focal epilepsy develops from numerous causes other than trauma to the brain. Abscesses, tumors and adhesions may cause this symptom complex.

*Hystero-Epilepsy*.—"Hystero-epilepsy," admittedly, is a poor term, but it is descriptive of one type of the disease and serves tentatively as a useful classification. We do not desire to enter into a discussion of the question as to the fundamental etiologic unity of the so-called hystero-epilepsy, affect epilepsy and alcohol epilepsy, which has

5. Foerster, O.: Encephalographische Erfahrungen, *Ztschr. f. d. ges. Neurol u. Psychiat.* **94**:515, 1924.

6. Wortis, S. B.: Head Injuries: Effects and Their Appraisal; Experimental Studies of Induced Convulsions and Ventricular Distortion in the Cat, *Arch Neurol & Psychiat.* **27**:776 (April) 1932.

7. Foerster, O., and Penfield, Wilder: The Structural Basis of Traumatic Epilepsy and Results of Radical Operation, *Brain* **53**:99, 1930.

been studied in detail by Notkin.<sup>8</sup> There are undoubtedly certain persons in whom convulsive attacks have developed after trauma who present one or more of the stigmas of hysteria or other evidence of functional nervous disorder; the attacks follow the types described by Osler<sup>9</sup> and other authors of textbooks as hysterical as opposed to truly epileptic, and the course and response to treatment are similar to other objective phenomena occurring in hysteria. We have included such forms under the term hysterio-epilepsy.

*Reflex.*—Reflex epilepsy is epilepsy with periodic attacks due to peripheral injury. It may be preceded by an amra. Removal of the peripheral scar stops the attack (Siemerling<sup>10</sup>).

It is noteworthy in reviewing the literature on epilepsy that there is a comparative lack of reports of cases of this type of epilepsy in the recent as compared with the earlier literature. This is perhaps due to a more scientific and accurate study of the cases, with consequent discovery of evidences of a cerebropathologic condition which is considered to be the probable cause of the convulsions. The record of a case of this type of epilepsy in a patient whom we have recently seen is as follows:

W. M., aged 37, a lumberman, eleven months before we examined him suffered an injury when a boom struck his right arm and chest, throwing him to the ground and causing complete paralysis of the right radial and left external popliteal nerves. Roentgenograms revealed a fracture of the right eighth, ninth, tenth and eleventh ribs in the axillary line, fracture of the superior and inferior rami of the pelvis on both sides and a comminuted fracture of the right ilium. Immediately following the injury the patient was operated on, and an attempt was made to suture the radial nerve. This nerve was again explored in December 1932 and scar tissue was removed. In February 1933 the external popliteal nerve was explored and found embedded in scar tissue. Several weeks before the last operation, the patient began to have attacks of jerking movements of the left leg. The attacks increased somewhat and became rather severe three weeks following the operation. The attacks came on spontaneously, although they could be brought on by galvanic stimulation over the scar of the operative incision. During examination a few days previous to the present writing an attack was brought on by galvanic stimulation in this area, which developed in the following manner: A few minutes after the current was applied the patient felt a peculiar sensation in his epigastrium. Very soon each muscle of the left thigh began to ripple. In a few seconds clonic contractions of the muscle fibers in this area appeared. After a few seconds of further contractions, the thigh flexed on the abdomen and the knee on the thigh. This spasm was tonic, and for a few minutes it was impossible for the leg to be passively extended. The arms became rigid at the sides of the body, and the elbows became flexed at a right angle. The patient complained of intense pain in the leg.

8. Notkin, J.: "Affecte Epilepsy" and "Hysteroepilepsy, Study of Convulsive States in Psychopaths, J. Nerv. & Ment. Dis. 72:135 (Aug.) 1930.

9. Osler, William: Principles and Practice of Medicine, ed. 11, revised by Thomas McCrae, New York, D. Appleton & Company, 1930.

10. Siemerling, quoted by Bowers, Paul: Traumatic Epilepsy, Internat. Clin. 4:132, 1921.

He was conscious during the entire attack and answered questions. The face was flushed, and the muscles of the neck were under tension. Finally, with the aid of an assistant, the leg was straightened, and the attack subsided immediately.

*Generalized Convulsions.*—In order to obtain more definite criteria for assistance in arriving at a final decision as to whether a head injury is the causative factor in questionable cases for the onset of generalized convulsions, we have reviewed 300 articles in the literature, from which we were able to collect 65 satisfactory case reports, and 7 case records of our own. In analyzing the records of cases, we have eliminated those which we considered to be of nontraumatic epilepsy; those of definite jacksonian character, in most of which the condition was due to bony spicules, abscess, intracranial hemorrhage or some other localized pathologic condition, and those of hystero-epilepsy and reflex epilepsy. An effort has been made to determine: (1) the relationship between the severity of the injury and the onset of the convulsions and (2) the time of onset of the convulsions.

#### REPORT OF CASES

CASE 1.—*History.*—L. G., an American, aged 27, a mechanic, reported for examination on Nov. 18, 1929, with the complaint of attacks of unconsciousness, headache and vertigo.

The patient's history and the family history were essentially unimportant.

Seventeen months previously the patient was struck on the head or the back by a falling timber (the witnesses differed as to whether the head or the back was struck). He became unconscious at once and did not remember anything until two weeks later; he was in the hospital for one month and was then discharged to return to work. After the injury he had attacks of frontal headache and dizziness which occurred especially when he was stooping. He tired easily, and occasionally objects became blurred before his eyes. He slept poorly. Memory was good for past events, but he was forgetful in carrying out orders. He had difficulty in holding positions as a mechanic because he fell asleep and did not carry out accurately a simple mechanical procedure.

Six months before presenting himself for treatment he began to have attacks of unconsciousness; he had eight such attacks in all. A definite aura always preceded them. Occasionally he felt that he was going away in a dream and became unconscious; at other times something seemed to be pulling him forward in terrific jerks and he became unconscious at about the third jerk. On one occasion he chased a friend around the room and tore his shirt off. His last attack was at home, two weeks before presentation. He called his brother, and when the latter arrived he was unconscious and rigid; his eyes were closed, his face red and his breathing rapid. This lasted three minutes; he then said a few words and went to sleep. It generally required about twenty-four hours for him to become normal after an attack, but he was up and about in an hour. He was often confused after this hour.

*Physical Examination.*—The patient was a well developed, well nourished man. The pulse rate was 86; the temperature, 98.6 F.; the blood pressure, systolic 125 and 80 diastolic; the height, 5 feet and 5½ inches, and the weight, 149 pounds (67.6 Kg.). He had several moles. The hair, eyes and ears were normal. The tonsils were buried and the pharynx reddened. The teeth were in good condition. The neck, heart, lungs, abdomen, spine and extremities were all essentially normal.

*Neurologic Examination.*—Cranial Nerves: There were fine tremors of the eyeballs on lateral, upward and downward movements. The corneal reflex was present. The condition was suggestive of, but not true, nystagmus. The pharyngeal reflex was diminished and the palatal reflex absent; otherwise the cranial nerves were normal.

Frontal Lobes of the Brain: The patient was apparently not exceedingly bright, but he appeared to be sincere. He was not of a quarrelsome nature, but when insulted would fight. However, he had had only a few fights. The other lobes of the brain were essentially normal. The patient had a strong grip, equal in the two hands.

Reflexes: The abdominal, patellar and achilles tendon reflexes were slightly exaggerated and equal on the two sides; otherwise all the reflexes were normal. There were no pathologic reflexes.

*Roentgen Examination.*—Roentgenograms revealed a fracture of the right occipital bone and also one of the right fourth and fifth metacarpal bones, with some union of the latter. Roentgenograms of the spine revealed no abnormalities.

*Diagnosis.*—The original injury was diagnosed as fracture of the skull, cerebral concussion and fracture of the right fourth and fifth metacarpal bones.

The later condition was diagnosed as posttraumatic cerebral syndrome, post-traumatic neurosis, possible posttraumatic epilepsy, with partial disability for work. Treatment with phenobarbital was instituted.

*Course.*—On December 6 there had been no attack of unconsciousness during the preceding three weeks. The memory was still poor; the dizziness and staggering gait had slightly increased, and the patient was drowsy during the day. We felt that the phenobarbital had probably stopped the attacks but had made him drowsy and increased the dizziness. The dose was decreased to  $\frac{1}{4}$  grain (0.016 Gm.) four times a day.

On December 19 the diagnosis of epilepsy was considered, to be confirmed. There had been no attacks since the first examination on Nov. 18, 1929, probably owing to the constant use of phenobarbital. The only complaint was occasional attacks of dizziness when the patient was quiet. The diagnosis was posttraumatic epilepsy and posttraumatic cerebral syndrome.

On Feb. 3, 1930, it was discovered that the patient had had two attacks of epilepsy since the last examination; one eleven days before and the other four days before, when he forgot to take his medicine. Physical examination and neurologic examinations gave the same results as at the first examination on Nov. 18, 1929. The patient was given phenobarbital,  $\frac{1}{4}$  grain (0.016 Gm.) three times a day and  $\frac{1}{2}$  grain (0.033 Gm.) once a day.

He was seen periodically until July 11, 1932. He was kept on phenobarbital, which was given in quantities small enough to avoid drowsiness, until Feb. 4, 1931, when the drug was discontinued and he was given a placebo. Since August 1930 he has apparently been able to do any kind of work on the ground. He had two convulsive seizures in June and July 1931, the first ones since February 1930, but he had none after that. He is now free from complaints. Recent physical examination and neurologic examinations revealed no abnormalities. He has received no sedative medication since February 1931. He was discharged on that date as well, without permanent disability.

CASE 2.—V., an American man, aged 42, an oil-worker, was struck on the right side of the face by a pair of tongs weighing 125 pounds (57 kg.). The right maxilla was fractured; there was no fracture of the cranium. The patient was unconscious for three minutes and dazed for three hours. Three weeks after the

injury he began to have attacks of petit mal, which would consist of momentary mental confusion, with loss of memory and inability to think or to comprehend what he was reading. These attacks have occurred from two to four times a day ever since they began. Eighteen months after his injury, the first grand mal attack developed. In the next twenty months the patient had about fourteen such attacks. The attacks are preceded by an aura, which does not occur with the petit mal attacks and which consists of a queer feeling, as of a "whirling around" in his head. If he is standing, he falls heavily and foams at the mouth. He becomes totally unconscious, has convulsive movements for two or three minutes and then passes into a stupor of varying duration. There is no history of an initial cry, of incontinence of urine or feces or of jacksonian attacks.

Physical examination revealed no abnormalities. The blood pressure was 102 systolic and 78 diastolic. The clinical and serologic tests gave negative results for syphilis; there were no signs of a tumor of the brain.

Twenty months after the injury, the patient was placed on a ketogenic diet and given medication with phenobarbital. For about six months he was free from grand mal attacks; then he became careless with his treatment and had one attack of grand mal. He was then free from attacks for eight months, during the last five months of which he did not follow the ketogenic diet but continued to take phenobarbital, bromide or other sedatives. This brings the case up to the present. A psychiatrist reported that the patient is retarded mentally. He has pursued no gainful occupation since his injury and is considered totally and permanently disabled.

CASE 3.—K. H., a Japanese boy, aged 12 years, was run over by a truck when he was 3 years old, the wheels going over his head. He was apparently normal until he was 6 years old, when he had an attack of scarlet fever, after which he soon began to have mild spells of unconsciousness. These were often accompanied by vomiting, cold perspiration and a cold, clammy appearance. They occurred about twice a year, each lasting from a few hours to a day, and have not changed appreciably in character or severity since they first appeared.

Twenty-four days ago, the patient had an attack at school and was unconscious for fifteen minutes. He did not bite his tongue or become incontinent or froth at the mouth. Soon afterward a severe headache developed which lasted all day. Six days ago the patient had another attack, in which he did not lose consciousness but became very dizzy.

Physical examination showed no abnormalities except chronic follicular tonsillitis, marked postnasal discharge, chronic pain and sinusitis, especially of the maxillary antrums.

Neurologic examination revealed that the pupils were moderately dilated and that there was nystagmus on looking laterally to the right and the left. The patient was oriented as to persons, place and time; cooperation and attention were good. There was no weakness or paralysis. The abdominal, cremasteric, patellar and achilles tendon reflexes were all exaggerated and equal on the two sides. The Wassermann test of the blood was negative; the blood count was normal.

An encephalogram showed that the right ventricle was moderately dilated and the left ventricle contracted. There was a deformity of the anterior horn of the left ventricle. A greater amount of air than is present normally appeared over the occipital area, which suggested cortical atrophy. A later examination will be necessary to determine if a tumor of the brain is developing.

An otologist carried out the vestibular tests and reported that the results were suggestive of a lesion involving the intracranial vestibular pathways. He advised that the vertical nystagmus upward, which appeared occasionally when the patient

gazed at an extreme angle upward, he watched. He had no suggestion to make as to the nature of the lesion; he thought that it might have been produced by a toxemia, such as the scarlet fever from which the patient had suffered. He recommended tonsillectomy and treatment of the sinusitis.

Only one observation has been made of this patient to date. A diagnosis of convulsive seizures secondary to unilateral hydrocephalus and cortical atrophy was made, and it was advised that the patient be given phenobarbital and a limited amount of fluids.

CASE 4.—G. S., a man aged 68, married, a painter, fell 8 feet (2.4 meters), sustaining a fracture of the left parietal bone, with extradural hemorrhage, and also a fracture of one scapula and of a great toe. Roentgenograms showed a comminuted fracture of the vault; no operation was done. The patient was in the hospital for several months; he was unconscious for three days following the injury. Blood flowed from the left ear at the time of injury.

Two months after the injury the patient was improving mentally, and the wound was draining; he had difficulty in speaking at times. Three months after the injury, in attempting to turn over quickly, he became dizzy. He still had some difficulty in speaking; his hearing in the left ear was impaired, and he was dizzy and nervous. Four months after the injury some teeth were pulled, and the jaw was curetted. Seven months after the injury he was improving; during the following month he was still dizzy. Eight and one-half months after the injury, while at work, he suddenly fell, becoming unconscious. Following this he had the first headache since his injury. Nine and a half months after the injury arteriosclerosis and nephritis were diagnosed, and some of the attending surgeons stated the belief that these conditions may have accounted for some symptoms. A week later, a shooting pain developed over the left side of the head, with dizziness, and he again fainted. Eleven months after the injury, while driving a truck, he became unconscious and drove into a telegraph pole. Two weeks later, he complained of tinnitus and of dizziness of moderate severity when lying on his right side. He also suffered loss of memory and was irritable. The biceps reflex was slightly more active on the right, as were the triceps and radial reflexes. There was no Babinski sign.

Fourteen months after the injury, while he was eating in a cafeteria, his head and eyes were drawn to the right side and he became unconscious and fell to the floor, biting his tongue.

Three months later he was given phenobarbital because of another epileptic fit.

The case was terminated nineteen months after the injury by a permanent disability rating by the Industrial Accident Commission of 78.5 per cent disability, based on dizziness, limited motion of the shoulders, loss of hearing and retinal hemorrhage. He received \$20.83 a week for forty weeks and a pension for the remainder of his life of \$5.93 a week.

CASE 5.—A. J. S., a man aged 51, sustained a depressed fracture of the left frontal bone and a stellate fracture of the base of the skull just posterior to the left mastoid process. The patient was unconscious for six days following the accident; four days after the accident a subtemporal decompression was done. Complete anosmia developed immediately after the injury and persisted permanently. For four months after the injury there were some mental confusion and moderate euphoria, and the patient was easily excited. These mental developments were superimposed on an original low grade mentality and some neurasthenia. Impairment of hearing was noted about a year after the accident, and it gradually increased over a period of twelve months following its first appearance, being more

marked on the left side. One year after the injury the patient showed slow cerebration and some defect in memory for events long past, and these persisted. Atrophy of the optic nerve on the left side was definitely diagnosed eight months after the accident. Twenty-five months after the accident there appeared for the first time epileptiform attacks with cramping of the arms, legs and stomach. The patient complained of headaches, vertigo and blurred vision in the left eye continuously after the accident.

On examination there was a slightly exaggerated patellar reflex on the left side; a slight increase in the left biceps and achilles reflexes lasted for a year following the injury.

The patient received a permanent disability rating from the Industrial Accident Commission of 100 per cent about thirty-five months after the accident, for industrial blindness of the left eye, anosmia, impaired hearing of both ears, mental deficiency and traumatic epilepsy.

CASE 6.—R. W. H., a man aged 40, an iron-worker, fell 15 feet (6 meters) sustaining a transverse fracture of the occipital bone. The patient was unconscious; he remained in the hospital for eighteen days. Forty-nine months after the accident, fainting attacks developed; he would perspire over his entire body, his face would become pale and he would feel weak and fall on his knees. His entire head seemed to throb before an attack.

Neurologic examination revealed no abnormalities at that time. He had attacks of headache. During the second attack, the patient had a peculiar taste in his mouth, and vision became blurred. During the third attack he also had a peculiar taste. The attacks were of only momentary duration, and he felt entirely well afterward.

Tests of the spinal fluid one month after the attacks began gave negative results.

The patient was given phenobarbital. Fourteen months after the attacks began, they ceased, but if the dose of phenobarbital was decreased the patient had an olfactory aura. He was observed for thirty-two months after the onset of attacks, and in the last eighteen months of that period he had experienced no attacks, but had been given phenobarbital, generally 2 grains (0.13 Gm.) a day. Toward the end of that period he returned to work as an iron-worker.

This case was considered to be one of posttraumatic epilepsy with aura, the attacks being of the petit mal variety, which developed long after the injury.

CASE 7.—F. S., a man aged 45, was admitted to the hospital on March 3, 1933, and discharged on the same day.

The patient had received an injury to the head twenty-five years previously. Since then he had had epileptic attacks frequently. During an attack everything turned dark before his eyes and he fell to the floor, frothing at the mouth and biting his tongue. He complained of headache after regaining consciousness. The attacks began from two to three years after the injury.

The physical condition of the patient was normal. The blood pressure was 110 systolic and 70 diastolic. An encephalogram was to be made, but for reasons unknown it was not done.

The spinal fluid was clear, with 4 cells; there was a slight increase in the globulin, and the Wassermann test was negative.

The diagnosis was posttraumatic epilepsy.

#### COMMENT

The study of the articles reviewed was begun with the purpose of obtaining data based on complete histories of cases, but this has been

extremely disappointing; the records of cases have been incomplete, details necessary for careful analysis being absent. In many instances no attempt has been made to differentiate focal epilepsy from generalized epilepsy. The majority of the articles are statistical summaries containing occasional records of cases. The conclusions drawn from single reports of cases in some instances have been biased and opinionated and not based on the facts presented by the case. However, aside from these difficulties, several excellent detailed reports comprising analytic studies of large numbers of cases of epilepsy, chiefly from bullet wounds received in war, have appeared in the literature of the last decade.

As may be noted from the following statistics, epilepsy occurs with sufficient frequency following injury to the head to be of

#### *Statistics on Epilepsy*

Author	Cases of Head Injury	Incidence of Epilepsy, Percentage	General	Focal
Rawling.....	452	25	14	6
Steinthal and Nagel.....	639	28.9		
Coleman.....	70	21		
Villandre.....	450	70		
Vogeler.....	1,334	16.5		
Forbes.....	229	15.1		
.....	266	12.5		
.....	4,262	10.14		
Villaret and Dalby.....	509	7		
Reichman.....	600	3.5		
Adle and Vagstaffe.....	610	6		
Neuhof.....	175	1.7		
Bowers.....	2,000	2.3		
Wilson.....	16,000	5		
Glaser and Shafer.....	325	5.8	1.8	1.5
Redlich (review of the literature)....	...	20	...	...
Cobb (review of the literature).....	...	4	...	...

clinical importance. On the other hand, there is a great variance in statistics as to the number of patients in whom posttraumatic convulsions develop.

In Rawling's<sup>11</sup> series of 452 cases of wounds of the head, epilepsy occurred in 25 per cent. The attacks in 57 per cent of the cases were generalized; in 25 per cent they were jacksonian.

Steinthal and Nagel<sup>12</sup> reported 639 cases of bullet wounds of the brain from injuries received in war, in 28.9 per cent of which typical epilepsy developed. In another 6.6 per cent of the cases the patient showed some epileptiform symptoms. Steinthal and Nagel divided their cases into primary cases, in which the epilepsy occurred at once or nearly so; i. e., either at the time of the injury or during the healing of the

11. Rawling, L. B.: The Remote Effects of Gunshot Wounds of the Head, *Brit. J. Surg.* **10**:93, 1922.

12. Steinthal, E., and Nagel, H.: Die Leistungsfähigkeit im bürgerlichen Beruf nach Hirnschüssen mit besonderer Berücksichtigung der traumatischen Epilepsie, *Beitr. z. klin. Chir.* **137**:361, 1926; **143**:35, 1928.



wound, and into secondary cases, in which the epilepsy occurred after healing. They found that 62.7 per cent of the cases of epilepsy belonged to the primary division and 37.3 per cent to the secondary. In 6.4 per cent of the epileptic patients the disease did not develop until four years or more after the injury.

Coleman<sup>13</sup> reported an incidence of epilepsy of 31 per cent in 50 cases of head injury.

Villande<sup>14</sup> reported epileptic seizures in 70 per cent of 450 cases of cranial wounds.

Vogeler,<sup>15</sup> in 1,334 cases of bullet wounds of the skull, found that epilepsy occurred in 16.5 per cent.

Redlich, quoted by Vogeler, in a review of the entire literature described traumatic epilepsy as occurring in from 15 to 20 per cent of the cases of wounds of the head.

Levinger,<sup>16</sup> of 229 cases of head injury, found that epilepsy developed in 13 per cent, while Frazier and Ingham<sup>17</sup> reported that of 200 cases of gunshot wounds of the head epilepsy developed in 12.5 per cent.

Tuffier and Gullian, quoted by Frazier and Ingham,<sup>17</sup> at the Third Interallied Congress held in Val-de-Grace, on Nov. 5, 1917, reported that epilepsy occurred in 10.14 per cent of 4,262 cases.

Cobb<sup>18</sup> stated that traumatic epilepsy occurred in about 4 per cent of cases of injury to the head.

Villaret and Bailby<sup>19</sup> found epilepsy in 7 per cent of 500 cases; Collier,<sup>20</sup> in from 5 to 8 per cent of his cases, and Reichmann,<sup>21</sup> in 3.8 per cent of 600 cases. Wagstaffe and Adie,<sup>22</sup> in a publication of the

13. Coleman, C. C.: The Late Results of a Series of Head Injuries, *Virginia M. Monthly* **48**:235 (Aug.) 1921.

14. Villande, C.: Healing of Skull Wounds, *Arch. de méd. et pharm. mil.* **68**:546 (Oct.) 1917.

15. Vogeler, K.: Das Spätschicksal der Schädelschussverletzten, *Deutsche Ztschr. f. Chir.* **234**:245, 1931.

16. Levinger, Louis: Untersuchungen an 30 durch Unfall Hirnverletzten mit epileptiformen Erscheinungen, *Arch. f. orthop. u. Unfall-Chir.* **31**:372, 1932.

17. Frazier, C. H., and Ingham, S. D.: A Review of the Effects of Gunshot Wounds of the Head, *Arch. Neurol. & Psychiat.* **3**:17 (Jan.) 1920.

18. Cobb, Stanley: Causes of Epilepsy, *Arch. Neurol. & Psychiat.* **27**:1245 (May) 1932.

19. Villaret, M., and Bailby, J.: Results in Five Hundred Cases of Cranial Cerebral Trauma, Ten to Twelve Years After Injury, *Presse méd.* **35**:290 (March 5) 1927.

20. Collier, James: Discussion of the Nature and Treatment of Epilepsy, *Brit. M. J.* **2**:1045 (Dec. 6) 1924.

21. Reichmann, V.: Occurrence and Frequency of Epileptic Seizures After Skull Fractures, *Deutsche Ztschr. f. Nervenhe.* **96**:260, 1927.

22. Wagstaff, W. W., and Adie, W. J.: Notes on a Series of One Hundred and Sixty-One Cases of Gunshot Wounds of the Head Treated at No. 7, General Hospital, May to Aug. 1916, *J. Roy. Army M. Corps* **31**:307, 1918.

Medical Research Committee of Great Britain, reported epilepsy in 6 per cent of 610 cases.

Neuhof<sup>23</sup> had "statements of epilepsy" in 3, or 1.7 per cent, of 175 cases.

Bowers,<sup>10</sup> in a review of 3,000 cases of head injury, found that the incidence of epilepsy was 3.3 per cent.

Wilson<sup>24</sup> found epilepsy in 5 per cent of 18,000 cases.

Glaser and Shafer,<sup>25</sup> on investigation of 325 cases, found traumatic epilepsy in 19, or 5.8 per cent; in 6, or 1.8 per cent of the total number, the attacks were generalized; in 5, or 1.5 per cent, they were focal, and in 8, or 2.4 per cent, the condition was diagnosed as hystero-epilepsy. We have described our seven cases of generalized traumatic epilepsy in detail earlier.

It has been determined by this analysis that generalized convulsions may occur within the first ten days after injury. The important factor in regard to these early convulsions is that in every case the injury was of great severity. Kaldewey,<sup>26</sup> from his investigation, decided that these cases are extremely rare. Vogeler,<sup>13</sup> in a review of 743 cases of gunshot wounds with 163 cases of epilepsy, found 18 in which early convulsions developed. Every patient had received unusually severe head injury which was associated with fracture of either the base or the vault.

Foerster, in 1926, stated that immediate epileptic attacks could follow trauma of the head but would occur only in cases of severe injuries, such as fracture, hematoma or foreign bodies within the brain.

One may conclude from our statistical study, as well as from the opinion of the various authorities, that early convulsions must be associated with severe injury to the brain. For this reason any case in which epileptic seizures of the generalized type develop after a minor injury, as in the case which we have reported, within a period of several weeks would immediately be excluded from the posttraumatic group.

Further investigation of these cases brought out only one outstanding feature: In all the cases in which generalized epilepsy developed, the injury was of great severity.

Muskens<sup>27</sup> stated the belief that the diagnosis of traumatic epilepsy must be reserved for cases in which a fracture of the skull exists.

23. Neuhof, Harold: Treatment of Craniocerebral Wounds and Its Results, *Ann. Surg.* **72**:556 (Nov.) 1920.

24. Wilson, S. A. K.: The Rôle of Trauma in the Etiology of Organic and Functional Nervous Disease, *J. A. M. A.* **81**:2172 (Dec. 29) 1923.

25. Glaser, M. A., and Shafer, F. P.: Skull and Brain Trauma; Their Sequelae, *J. A. M. A.* **98**:271 (Jan. 23) 1932.

26. Kaldewey, W.: Zur Frage der Frühepilepsie nach Unfall, *Monatschr. f. Unfallh.* **37**:161 (April) 1930.

27. Muskens, L. J. J.: *Epilepsy*, New York, William Wood & Company, 1928.

Fracture of the skull or unconsciousness for a relatively long period existed in all the cases. None of the patients had merely a slight laceration of the scalp. In very few of the cases did generalized epilepsy develop within the first five or six months, except in those cases in which it developed within the first ten days. The generalized epileptic seizures developed six months or more after the injury. In the article by Vogeler it was reported that the convulsive seizures developed primarily in a period of from six months to two years after the injury, but additional cases developed at an average rate of 0.22 per cent, or 1 in 445, until the seventeenth year after the injury. This was also found by us.

Throughout the literature there are numerous reports of cases of epilepsy developing at this late period. Of course it is difficult to ascertain the relationship between an alleged head injury and epilepsy which has developed about seventeen years afterward. From the war statistics it appears that this is possible.

It is the belief of some authors, though without substantiation, that the production of epilepsy is dependent on a special tendency for spasms to develop in a particular person and that the injury acts merely as an exciting or culminating factor.

It is apparent from our studies that posttraumatic generalized epilepsy may occur within the first ten days or so following a head injury in which the trauma is markedly severe and that in a period of from five to six months thereafter it does not often occur. Any case in which generalized epilepsy develops during that period should not be classified as of traumatic origin until such an origin is definitely proved. This fact is of interest from a pathologic standpoint and fits in with the development of changes in the brain (Naffziger and Glaser<sup>28</sup>).

The majority of the convulsive seizures develop within the first two years after injury. Posttraumatic epilepsy is rare. It occurs in approximately from 1.5 to 4 per cent of the cases. That it appears only in cases of severe trauma is to be expected, for, should it be prevalent in cases of minor head injuries, it would develop in practically every child.

#### PATHOLOGY

Injuries of the head may bring about various pathologic changes within the brain. It is impossible to state that many of them may be related to succeeding epilepsy. Which of these pathologic changes are responsible for late epilepsy one cannot state with any certainty. The literature has not revealed uniform pathologic changes which could account for the development of generalized epilepsy. For this reason,

28. Naffziger, H. C., and Glaser, M. A.: *An Experimental Study of the Effect of Depressed Fractures of the Skull*, *Surg., Gynec. & Obst.* 51:17 (July) 1931.

we have briefly considered the various organic changes which are known to exist in the brain following trauma. It is possible that any of these may be responsible for generalized epilepsy, yet, on the other hand, it may again be true that such epilepsy, secondary to trauma of the head, may occur in a perfectly normal brain. These points to date have not been verified by a sufficiently extensive statistical study to justify any conclusions.

Much of our knowledge of the pathology of concussion is deduced from the more serious cases of head injury. There is the work of Trotter,<sup>29</sup> Head,<sup>30</sup> Cushing,<sup>31</sup> Mott,<sup>32</sup> Meyer,<sup>33</sup> Cassasa,<sup>34</sup> Adami<sup>35</sup> and Foix.<sup>36</sup>

There are numerous theories as to the mechanism by which these pathologic changes may be brought about. This is not within the scope of this paper.

Trotter and Head have described opacity of the arachnoid with slight distention from the fluid beneath. The brain is orange-colored as a result of extravasation of blood. This is found in cases of old unresolved contusions. In the more severe cases of brain injury, as described by Cushing, there is actual disorganization of the substance of the brain, with severe intracerebral hemorrhage.

Adolph Meyer described small foci of softening, or defects of the cortex, in the tips of the frontal or temporal lobes.

Cassasa described 5 cases which seemed to be true cases of concussion. At autopsy gross section showed many minute hemorrhages scattered throughout the brain, including the cerebellum. Microscopic examination showed areas of hemorrhage limited to the perivascular lymph spaces and others also within the immediate adjoining substance of the brain.

Osnato and Giliberti<sup>37</sup> remarked that the appearance of microscopic sections showed a striking similarity to the perivascular extravasation observed in epidemic encephalitis.

29. Trotter, Wilfred: *Shell Wounds of the Head, Brain* 42:353, 1919.

30. Head, Henry: *Shell Wounds of the Head, Brain* 42:349, 1919.

31. Cushing, Harvey: *A Study of a Series of Wounds Involving the Brain and Its Enveloping Membranes*, *Brit. J. Surg.* 5:565, 1918.

32. Mott, F. W.: *War Neuroses and Shell Shock*, New York, Oxford University Press, 1919, pp. 4, 5 and 38.

33. Meyer, Adolf: *The Anatomical Facts and Clinical Varieties of Traumatic Insanity*, *Am. J. Insanity* 6:374, 377, 382 and 388 (Jan.) 1904.

34. Cassasa, C. B.: *Multiple Traumatic Cerebral Hemorrhages*, *Proc. New York Path. Soc.* 24:101 (Jan.-May) 1924.

35. Adami, J. G., and Nicholls, A. G.: *Principles of Pathology* ed. 2, London, H. Frowde, vol. 2, p. 575.

36. Foix, Charles: *Traumatic Lesions of the Skull and Brain*, in *Nelson Looseleaf Medicine*, New York, Thomas Nelson & Sons, 1920, vol. 6, p. 145.

37. Osnato, Michael, and Giliberti, V.: *Postconcussion Neurosis; Traumatic Encephalitis*, *Arch. Neurol. & Psychiat.* 18:181 (Aug.) 1927.

Tanzi,<sup>38</sup> in cases in which the condition was classified as dementia traumatica, described small old hemorrhagic foci, transformed into cysts or into glial scars, diffuse chronic lesions of the nervous elements and chronic diffuse lesions of the vessels. He expressed the belief that following trauma lesions occur which later develop into the chronic processes of gliosis and degeneration.

With these changes, as described by Cassasa, it cannot but follow that certain mental and somatic symptoms will occur, developing with the secondary diffuse degeneration of glial and ganglion cells. The degree of this secondary diffuse process should determine the clinical phenomena that is interpreted as the posttraumatic cerebral syndrome. From experimental evidence, presumably the brain is sensitized so that sooner or later environmental influences produce additional symptoms which may be classified as psychoneurotic and are superimposed on the symptoms of the posttraumatic cerebral syndrome. This may result in hystero-epilepsy.

Naffziger and Glaser,<sup>39</sup> in experimentally produced cases of depressed fracture of the skull in rabbits, in which the animals were followed for a period of a year or more, demonstrated early cortical vascular changes due to the acute effects of the trauma. The acute pathologic condition cleared up within six weeks. At the end of eight months, deep-seated glial changes were noted directly beneath the site of injury, over the corpus callosum. The experiments were controlled by another set of animals in which depressions of the brain were produced by beads rather than by depressed fractures. In these no evidence of glial proliferation occurred. It is interesting to note that the clinical development of epilepsy occurs late and that the glial changes in the animals occurred late. What significance the deep-seated glial changes have in relation to the production of posttraumatic epilepsy has yet to be demonstrated, but the time limit is suggestive. There is a possibility that in post-traumatic epilepsy deep glial changes do occur over the corpus callosum, as in the animals.

Fay and Winkelman,<sup>39</sup> as the result of the observations of Bagley<sup>40</sup> that blood introduced into the subarachnoid space caused adhesions, expressed the belief that the pacchionian bodies were injured, with a resulting obstruction to the absorption of spinal fluid which caused secondary pressure atrophy of the cortex.

---

38. Tanzi, Eugenio: *A Text-Book of Mental Diseases*, translated from the Italian by W. Ford Robertson and T. C. Mackenzie, New York, Rehman Co., 1909.

39. Fay, Temple, and Winkelman, N. W.: Pacchionian System; *Histologic and Pathologic Changes with Particular Reference to Idiopathic and Convulsive States*, *Arch. Neurol. & Psychiat.* 23:44 (Jan.) 1930.

40. Bagley, Charles: *Functional and Organic Alterations Following the Introduction of Blood into the Cerebrospinal Fluid*, *A. Research Nerv. & Ment. Dis., Proc.* 8:217, 1927.

Spielmeyer<sup>41</sup> has found in cases of epilepsy, whether essential or traumatic, changes within the cornu ammonis and the cerebellum. The changes were in the form of sclerosis. The sclerosis had the appearance of a thick, glial proliferation. In addition, there was loss of ganglion cells in definite areas. These were the late changes. Spielmeyer stated the belief that the relatively unsatisfactory blood supply to these parts causes them to suffer first, whereas in other parts of the brain, because of compensatory circulation, less reaction to the disturbance occurs. As all organic sources of these disturbances have been excluded, one must conclude that the vasomotor changes are influential in the mechanism of the epileptic attacks. As there is no evidence of stasis, the source must be vasospasm. This compares with the observations of Horsley, Dandy, Kennedy, Horrax and others, who have described sudden anemia and a decrease in the size of the brain at the beginning of each attack during exploratory craniotomy. These observations do not state the essential cause of the attack, but they help us to draw some conclusions about the mechanism.

Directly due to trauma there may be focal lesions with actual destruction of the brain, as has been described earlier in this paper. In addition, the immediate effect of generalized edema of the brain should be recognized. Rand and Courville<sup>42</sup> in fatal cases of injury of the head found increased vacuolation of the choroid epithelium and of the ependymal cells, with a variable degree of edema and with heightening of the individual cells. Occasional hemorrhagic extravasation was observed, but more frequently there was pigment in the stroma and epithelial vacuoles.

All these pathologic changes are secondary to hemorrhage, and the late effects are dependent on degenerative adhesions or glial proliferation secondary to the original hemorrhage. Were one to consider these pathologic changes the cause of the convulsions, there would be many more cases of epilepsy than exist. As one knows in proportion to the tremendous number of head injuries that occur epilepsy is in the minority and occurs following only the more severe type of injury.

The fact that a head injury sensitizes the brain so that extraneous circumstances may more readily bring on convulsions was shown by the work of Sauerback in 1913, who found that after trauma to the motor cortex smaller doses of cocaine produced convulsions than would produce convulsions in normal control animals. Dandy and Elman<sup>43</sup>

41. Spielmeyer, W.: Anatomic Substratum of the Convulsive States, *Arch. Neurol. & Psychiat.* **23**:169 (May) 1930.

42. Rand, C. W., and Courville, C. B.: Histologic Studies of the Brain in Cases of Fatal Injury to the Head, *Arch. Surg.* **23**:357 (Sept.) 1931.

43. Dandy, W. E., and Elman, Robert: Studies in Experimental Epilepsy, *Bull. Johns Hopkins Hosp.* **36**:40 (Jan.) 1925.

showed the same phenomenon, using absinth as a convulsant. Pike,<sup>44</sup> Muskens,<sup>27</sup> Wortis and McCulloch<sup>45</sup> and Wortis<sup>6</sup> confirmed this.

Jones and Langdon,<sup>46</sup> in the vestibular studies of epileptic patients, have found vestibular impairment and abnormalities. In practically all of these cases the vestibular deficiency was central; there was a subnormal constitutional response in 20 of 28 cases after turning, and after douching the constitutional responses were subnormal in 21 of 28 cases.

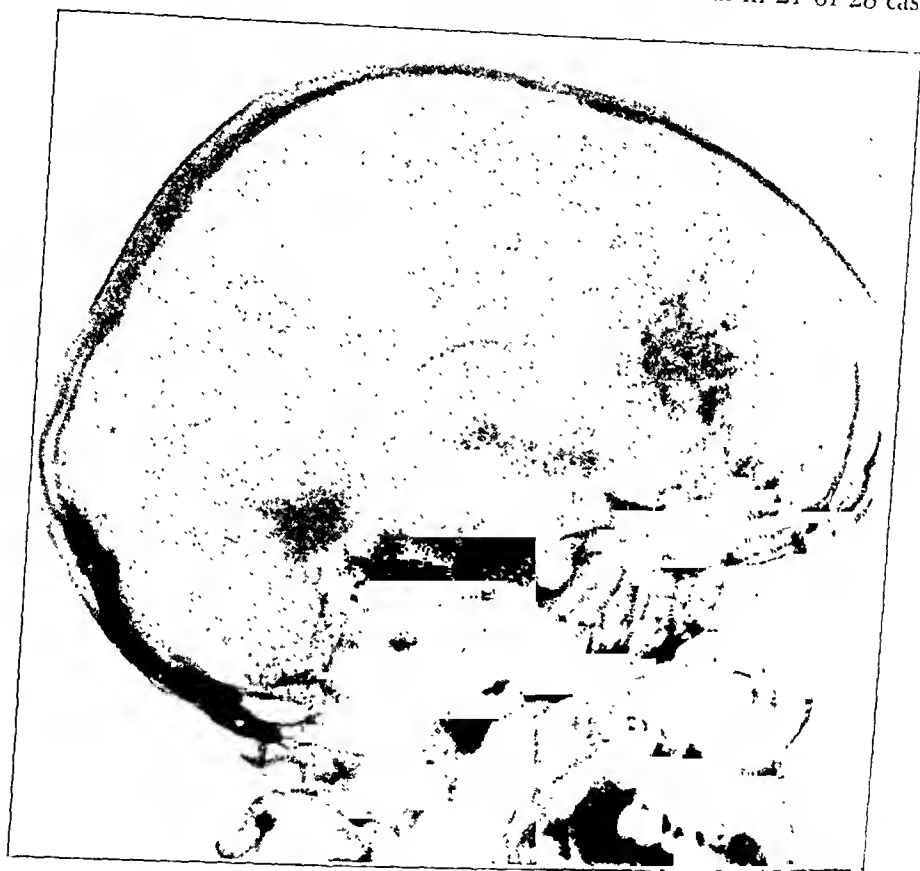


Fig. 1.—Roentgenogram showing posttraumatic epilepsy secondary to a depressed fracture of the skull. There are contraction of the ventricles and also cortical atrophy.

Rand and Linthicum,<sup>47</sup> while making a study of 35 cases found definite evidence of vestibular abnormalities. Glaser in a study of 65 cases

44. Pike, F. H., and others: Some Observations on Experimentally Produced Convulsions, *Am. J. Psychiat.* **10**:67 (Jan.) 1931.

45. Wortis, S. B., and McCulloch, W. S.: Head Injuries; An Experimental Study, *Arch. Surg.* **25**:529 (Sept.) 1932.

46. Langdon, H. M., and Jones, I. H.: Intimate Relations Between the Ear and Eyes, as Shown by the Bárány Tests, *Arch. Ophth.* **47**:348 and 354 (July) 1918.

47. Rand, C. W., and Linthicum, F.: Neuro-Otological Observations in Concussion of the Brain, *Arch. Otolaryng.* **13**:785 (June) 1931.

also found vestibular changes in 75 per cent of the patients. Of course no conclusions can be drawn from these findings other than that abnormalities existed which would indicate some disturbance in the central vestibular pathways.

Encephalographic changes in the form of distortion of the ventricles, unequal ventricles, atrophy or arachnitis have been found (figs. 1 to 4).



Fig. 2.—Roentgenogram showing posttraumatic epilepsy with a ventricular shift secondary to cerebral trauma and cortical atrophy.

It is true that in many of these cases there was a normal encephalographic picture. Grant,<sup>48</sup> in a review of 123 cases of epilepsy, of which 51 were posttraumatic, found that in 9.8 per cent of the traumatic group the encephalograms were normal. Atrophy and arachnitis were equally divided, while ventricular asymmetry occurred in 5.9 per cent of the idiopathic group and in 45 per cent of the traumatic group. It can

48. Grant, F. C.: Ventriculography and Encephalography, *Arch. Neurol. & Psychiat.* 27:1310 (June) 1932.



thus be noted that normal encephalograms, as well as ventricular asymmetry, predominate in the posttraumatic group.

Encephalograms are also of value in ruling out the presence of a tumor of the brain as the cause of epilepsy. In 2 cases under our observation epilepsy was a predominant symptom following a head injury. Later studies revealed the presence of a tumor of the brain, thus eliminating the preceding trauma as the cause of the epilepsy.



Fig. 3.—Roentgenogram showing posttraumatic epilepsy with inequality of the size of the ventricles and cortical atrophy.

For medicolegal purposes the encephalogram has only suggestive value in the differentiation of posttraumatic from idiopathic epilepsy. No definite statement can be made.

#### THERAPEUTICS

It is not within the scope of this paper to enter into a discussion of the therapeutics of epilepsy. However, two methods may be mentioned:

(1) the operative excision in cases of focal epilepsy, as described by Foerster and Penfield, and (2) encephalography for its therapeutic value. Grant, in reporting 51 cases of traumatic epilepsy, the progress of which in regard to convulsions has been followed from twelve months to two years, reported 12 in which the patient was completely relieved, 10 in which the patient was partially relieved, 17 in which the patient was unimproved and 12 in which the outcome was fatal. In the 39 cases



Fig. 4.—Roentgenogram showing posttraumatic epilepsy with a ventricular shift and cortical atrophy.

which he followed, 22, or 55.6 per cent, of the patients showed definite improvement; 17, or 43.5 per cent, showed no improvement. For this reason the question of encephalography, both as a differential diagnostic measure in distinguishing cases of an organic pathologic condition, such as tumor of the brain, from those of traumatic epilepsy and as a therapeutic measure, should be considered in cases of posttraumatic epilepsy. Similar results have been obtained by Fay, Pancoast, Pendergrass, Bingle and Glaser..

## CONCLUSIONS

A statistical study of cases of head injury reveals a wide discrepancy in the percentage of incidence of generalized epilepsy following trauma of the head. A careful analysis of these articles from our own personal experience indicates that the most likely incidence is in the neighborhood of 2.5 per cent in the cases of more severe head injury.

A statistical study indicates that epilepsy does not develop after minor, but follows only severe, head injury and generally occurs only in cases in which there has been fracture of the skull.

Generalized epilepsy may develop within the first ten days after head injury, provided the injury is of excessive severity.

Posttraumatic epilepsy occurs most frequently from six months to two years after the injury, less frequently from two to seven years afterward and infrequently from seven to twenty years afterward.

In attributing the epilepsy to trauma, all extraneous factors must be ruled out, particularly a history of convulsions prior to the trauma. Thorough physical and neurologic examinations should be made in order to establish that there is no organic, physical or neurologic disease and no mental condition other than the effects of the trauma causing the convulsions. In cases in which the first convulsion occurs at the time of the injury, special care in getting a detailed history is necessary to make certain that the injury did not happen because of the onset of an attack of idiopathic epilepsy.

Convulsive seizures developing in the first six months after minor head injuries should be considered psychoneurotic in origin, and every effort should be made to rule out such an etiology before the condition is diagnosed as true epilepsy. These statistical studies and our case reports have indicated the psychoneurotic character of such seizures, particularly in the cases of minor head injury.

We know of no method of preventing the occurrence of generalized epilepsy following head trauma other than the utilization of the accepted methods of treatment of the original injury.

Unless there is some special contraindication, we believe that encephalograms should be made in every case of posttraumatic epilepsy, both because they may have definite therapeutic value and because they may give further information of marked value in outlining further advisable steps for treatment; in some cases they have shown evidence that open operation should be performed.

# INJURIES TO THE CRUCIAL LIGAMENTS

HENRY MILCH, M.D.

NEW YORK

Injuries to the crucial ligaments have been considered among the more serious internal derangements of the knee joint, and a great deal of surgical thought and work has been directed toward obviating the ill effects of these injuries. At the outset, Mayo-Robson<sup>1</sup> and others attempted simple suture of the torn ligament. Later silk, then wire and finally fascia wrapped about silk were used to replace the torn ligament. However, Sir Robert Jones called attention to the fact that in complete dislocations of the knee, rupture of both crucial ligaments had to be predicated, and he expressed the opinion that the good results, when present, were due to the effects of prolonged rest rather than to the repair of the torn ligaments. In 1917, Hey Groves<sup>2</sup> published the description of his operation for the reconstruction of the ruptured anterior crucial ligaments. Though it effected a great improvement of the surgical results, the operation did not appear to be entirely satisfactory until its modification by the addition of the Alwyn Smith<sup>3</sup> procedure, which was designed for the repair of the tibial collateral ligament and which later was accepted by Hey Groves.<sup>4</sup> This combined operation has given some excellent results in my hands, as well as in the hands of other surgeons. The main drawback has been that the operation is complicated and requires considerable technical skill. This, taken in conjunction with other considerations, which will be noted later, has led to a review of the subject, particularly with the view of determining whether the disability is due entirely to injury of the crucial ligament and whether, in that event, the Groves-Smith operation is the method of necessity.

In spite of much that has been written about the functions of the crucial ligaments, there is still far from unanimity of opinion on the subject. From a consideration of the size and strength of the crucial ligaments, it appears reasonable to infer that they develop in response to powerful stresses and strains and that they perform a valuable and necessary rôle in the economy of the knee joint. But just what this rôle may be is problematic. Some investigators think that the crucial ligaments act merely as ligamenta teres, binding the tibia and femur

---

From the service of Dr. Harry Finkelstein at the Hospital for Joint Diseases.

1. Mayo-Robson, A. W.: *Ann. Surg.* 37:716, 1903.

2. Groves, E. W. H.: *Lancet* 2:674 (Nov. 3) 1917.

3. Smith, Alwyn: *Brit. J. Surg.* 6:176, 1918.

4. Groves, E. W. H.: *British J. Surg.* 7:505 (April) 1920.

together, and others consider that they are the true posterior ligaments of the knee joint, while still others believe that they represent the vestiges of ligaments which originally united two separate tibiofemoral joints. The majority, however, are of the opinion that these ligaments are the main, if not the sole, means of maintaining the stability of the joint. Since it is on the question of the significance of these ligaments that the rationale of the surgical therapy depends, a brief résumé of the knowledge on this subject will be condoned.

Information as to the function of the crucial ligaments has been gained through three main sources: (1) the study of their anatomic configuration and apparent physiologic action in the cadaver; (2) the experimental production on the cadaver of injuries to one or more of the ligaments of the knee joint and the determination of the disabilities so occasioned, and (3) the clinical study of patients.

Anatomically, by the obliquity of their direction, the crucial ligaments seem specifically designed to prevent displacement of the tibia in an anteroposterior direction. The anterior crucial ligament, attached above to the outer condyle of the femur and running downward, forward and medially to the depression in front of the tibial spine, appears to act as a check to forward displacement of the tibia. The posterior crucial ligament, coursing downward, backward and laterally from its attachment on the inner femoral condyle, appears to function as a check to backward dislocation of the tibia. Since forward tibial displacement normally occurs during extension and backward displacement during flexion, it has been believed that the anterior crucial ligament is tense only during extension while the posterior crucial ligament is tense only during flexion. The more careful studies of Weber,<sup>5</sup> Meyer,<sup>6</sup> Fick<sup>7</sup> and others have demonstrated that this is far from the truth.

It appears that, in its normal function, motion of the knee may be divided into two components; a flexion-extension motion, which occurs around a transverse axis, and a rotatory motion, which takes place mainly in extreme extension or in extreme flexion around a vertical axis. During the rotatory motion the crucial ligaments, acting together, prevent excessive internal rotation of the tibia, but neither plays a part in the absence of the other. This is due to the fact that during flexion the posterior crucial ligament acts as a stay around which the anterior winds and, thus becoming taut, hinders undue internal rotation of the

---

5. Weber, W. E., and Weber, E. F.: *Mechanik der menschlichen Gewerkezeuge*, Göttingen, Dieterich, 1836; quoted by Fick<sup>7</sup> and Pagenstecher.<sup>8</sup>

6. Meyer, G. H.: *Die Statik und Mechanik der Gelenke*, Leipzig, Wilhelm Engelmann, 1873, p. 368.

7. Fick, R.: *Anatomie und Mechanik der Gelenke*, in *Bardleben, K. H.: Handbuch der Anatomie*, Jena, Gustav Fischer, 1904, p. 521.

tibia on the femur. During the act of normal flexion and extension, parts of both crucial ligaments are tense throughout the movement, different parts becoming taut during different states of the motion, as may be gathered from the table devised by Fick.

In hyperextension, too, the anterior crucial ligament given herewith was found to be taut. It was found that in the alternation between flexion and extension the position of maximum tension on both crucial ligaments was that of flexion and internal rotation of the tibia on the femur. From these considerations it appears reasonable to conclude that the crucial ligaments function mainly during the act of flexion and that during extension the support of the knee is undertaken by other structures, viz., the collateral ligaments and the muscles about the joint.

In the main these anatomic findings have been substantiated by the evidence obtained through experimentation on the cadaver. Weber<sup>8</sup> showed that if the collateral ligaments of the knee remain intact and the crucial ligaments are cut, the knee retains its stability in extension. In

*Tension of the Crucial Ligaments*

	Fibers	Extension	Midposition	Flexion
Anterior.....	Anterior Posterior	Taut Relaxed	Taut Relaxed	Relaxed Taut
Posterior.....	Anterior Posterior	Relaxed Taut	Taut Relaxed	Taut Relaxed

flexion, however, the knee becomes unstable in the same sense as that if the anterior crucial ligament alone is cut the tibia can be displaced forward while if the posterior crucial ligament is cut backward displacement of the tibia becomes possible. On the other hand, if the crucial ligaments remain intact while only the collateral ligaments are cut, the stability of the knee is preserved during flexion but lost during extension. Pagenstecher<sup>8</sup> showed that with the knee flexed over a bolster rupture of the anterior crucial ligament results when the head of the tibia, struck from behind, is driven forward, while a rupture of the posterior crucial ligament occurs when the blow is delivered in front. Honigschmied<sup>9</sup> demonstrated the following facts: 1. Hyperextension of the knee results in injury to the tibial collateral ligament. However, he cited two cases reported by Stark in which rupture of the crucial ligaments occurred. If extension is continued after this first the anterior and then the posterior crucial ligament is ruptured. 2. Hyperflexion of the knee is normally impossible because of the interposition of the soft tissues. If a wedge is placed behind the knee, hyperflexion over this bolster brings about tearing of the anterior crucial ligament. 3. Hyper-

8. Pagenstecher: Deutsche med. Wchnschr. 29:872, 1903.

9. Honigschmied, J.: Deutsche Ztschr. f. Chir. 36:587, 1893.

adduction or hyperabduction of the tibia results in injury to the crucial ligaments only after preliminary tearing of the collateral ligaments. 4. Hyperpronation, i. e., internal rotation of the tibia, and hyper-supination, i. e., external rotation of the tibia, occasion damage to the capsule, the collateral ligaments or the menisci before causing lesions of the crucial ligaments. Pringle<sup>10</sup> succeeded in tearing the anterior crucial ligament by fixing the pelvis and then flexing, abducting and internally rotating the leg at the knee. He then noted that in such cases he "always found a degree of tearing of the internal lateral ligament at its deep or articular aspect; it never was complete; that is to say, it never involved the superficial fibers and none of the other ligaments of the joint showed any degree of injury. With the short fibers of the internal lateral ligament ruptured, it is not only possible but probable that a greater degree of abduction would be permitted than if they were intact."

As a consequence of these observations, two tests have been devised, which were believed to reveal injuries of the anterior crucial ligament<sup>11</sup> and which were believed to render the establishing of a diagnosis of rupture of this ligament an elementary matter. The first of these, the extension test, based on the experiments of Pagenstecher, Honigschmied and Pringle, is described by Jones and Smith<sup>12</sup> in the following words: "If, after an injury to the knee, the tibia can be displaced backwards or forward or rotated inward in the extended position, an injury to one or both crucial ligaments may be diagnosed." This statement is in complete contradiction of Weber's experiments and can be reconciled with clinical experience only if it is admitted categorically that every injury to either of the crucial ligaments is invariably associated with injury to the collateral ligaments. This, of course, is not the case. There is no doubt that isolated injuries to either the collateral or the crucial ligaments may occur. In the typical case, injury to the collateral ligaments can readily be diagnosed by the demonstration of abnormal lateral mobility with the knee in extension. The difficulty in diagnosis arises when lesions of both structures are present. In some instances only lateral instability, the characteristic sign of injury to the collateral ligament, is found, as will be seen from a study of the two cases reported by Pringle. In both, the erroneous diagnosis of rupture of the internal lateral ligament was made, but at operation an avulsion of the medial tibial spine was found in one case and a tear of the anterior crucial ligament in the other. In neither of these cases was

10. Pringle, J. Hogarth: *Ann. Surg.* 46:169, 1907.

11. Because of the relative rarity of injuries to the posterior crucial ligament, the majority of commentators confine themselves to discussions of injuries to the anterior crucial ligament.

12. Jones, R., and Smith, A.: *Brit. J. Surg.* 1:70, 1913.

there a rupture of the superficial fibers, but it was presumed that the deep fibers of the lateral ligament were involved. There was slight anteroposterior mobility in the second case during the anesthesia. The good results of simple suture in these cases can be explained only on the assumption that satisfactory healing of the lateral ligaments had occurred. Instead of demonstrating the presence of injury to the crucial ligaments, this test establishes conclusively only the additional loss of integrity of the tibial collateral ligament. The insistence of many surgeons that in the absence of a positive reaction to the extension test surgical intervention is contraindicated appears to be well grounded in the sense that only the patients who give a positive reaction show a degree of disability due to lateral instability sufficient to justify operation.

The second of the two tests, a fixation test, is characterized by the *signe de tiroir* of Rocher, or what may be purposely miscalled the "rocker" sign. It is elicited by fixing the foot with the knee in flexion. The upper end of the leg is grasped, and it will then be noted that in the event of a tear of the posterior crucial ligament the head of the tibia can be displaced abnormally forward. When the results are positive, this test is reliable, especially in cases in which a history of trauma has been obtained. Unfortunately, the sign is reputed to have been present in only one of about eight cases in which at operation ruptures of the crucial ligament have been found. All who have had the opportunity of operating on many knee joints have undoubtedly had the unpleasant experience of discovering lesions of this sort which were not suspected before arthrotomy because of the complete lack of symptoms of either anteroposterior or lateral hypermobility. In one case in which operation was performed recently the patient presented symptoms, such as locking, that were suggestive of an injury to the medial semilunar cartilage, but there was no evidence of preternatural mobility.

#### REPORT OF CASES

CASE 1.—*Repair of the anterior crucial and tibial collateral ligaments by the method of Hey Groves and Smith.*

L. S., a woman, aged 42, was admitted to the hospital on Jan. 19, 1932. There was a history of rheumatism twenty years previously, with repeated giving-way of one knee, associated with locking. About twelve days before admission to the hospital, the patient twisted her knee; she had since complained of pain, swelling and limitation of both flexion and extension. There was a moderate effusion into the joint, with a slightly positive "rocker" sign. In the extended position the knee was stable in all directions. There was definite tenderness over the anterior horn of the medial semilunar cartilage, with accentuation of pain on extension of the knee. The roentgen examination was reported as giving negative results. This, in conjunction with the aforementioned signs and symptoms, led to a diagnosis of fracture of the semilunar cartilage, for which operation was advised.



On January 21 the joint was opened through a median parapatellar incision. After evacuation of a moderate amount of fibrin-flaked fluid, it was noted that the anterior crucial ligament was torn from its tibial insertion and was so frayed that suture was impossible. A typical operation by the method of Hey Groves and Smith was performed. The fascial graft for the repair of the tibial collateral ligament was accurately placed over the anterior portion of the internal lateral ligament and was drawn particularly taut by gentle forcing of the leg into adduction. The wound was closed, and a plaster of paris bandage cast applied, with the knee in slight flexion. The patient pursued an uneventful postoperative course, and the leg was released from the cast at the end of about six weeks. She immediately complained that there was something "awfully tight" about the inner aspect of the knee which interfered with flexion. Physical therapy was started, and a knee-cage brace applied. Within a relatively short time the range of flexion gradually began to increase, so that at the present time the patient is able to bend the knee to slightly beyond a right angle. The power of extension is complete, and the patient has never since noted any instability or symptoms of giving way or locking of the joint.

A somewhat similar situation has been observed in cases of avulsion of the internal tibial spine. In uncomplicated cases, in which concomitant tearing loose of the anterior crucial ligament is almost invariably found, the "rocker" sign is negative, and diagnosis is impossible, except by noting the development of the symptom of bone block or by the study of the roentgenogram. Taylor<sup>13</sup> reported a case in which a pyriform osteoma, 3 by 5 by 7 cm., was disclosed by the roentgenogram. At operation, "there was a small sesamoid bone attached by a ligamentous band to the posterior extremity of this large osteoma. This ligamentous band was evidently the anterior crucial ligament, which had been torn loose from its tibial attachment, and in it the osteoma developed." This patient apparently suffered no symptoms from the tearing of the crucial ligament and suffered none after its removal. But for the limitation of extension, due to the gradual increase in the size of the intra-articular mass, undoubtedly derived from the avulsed tibial spine, the patient might never have become aware of any difficulty. The following case is fairly typical of this type of injury.

*CASE 2.—Suture of the anterior crucial ligament.*

V. R. was seen on March 4, 1930, more than six weeks after he had fallen about 12 feet (3.6 meters), landing on his feet and then falling forward and striking the flexed right knee. Immediately after the accident he complained of severe pain and inability to extend the knee or to bear his weight. A roentgenogram taken shortly afterward showed a "fracture of the knee joint," and a posterior splint was applied for one week. At the end of this time the patient was unable to walk, and aspiration of the knee, baking and massage were instituted, without any improvement. When first seen the patient walked with a marked limp. The knee joint was moderately distended by fluid and could not be completely extended (extension was possible to 170 degrees; flexion, to 70 degrees). There was no hypermobility in the anteroposterior or lateral direction, either in the extended

13. Taylor, R. Tunstall: *Ann. Surg.* 37:84, 1903.

or in the flexed position of the leg. Roentgenograms showed "a complete fracture of the medial crucial spine, with slight rotation and anterior displacement of the fragment."

On March 6 arthrotony was performed through a median parapatellar incision. The intercondylar space was filled with a thick pannus; the synovial membrane was thickened and congested; the medial crucial spine and the anterior crucial ligament were found to be torn from the tibial insertion and adherent to the granulation tissue in the intercondylar space. The bone fragment was pried loose from this mass and was then detached from the lower end of the anterior crucial ligament, which with great difficulty was sutured to the head of the tibia. With the patient under anesthesia there was a suggestion of a positive "rocker" sign, but this had completely disappeared by the time motion of the knee was started. On March 25 the patient was permitted to be up and about; there was apparent good stability in the knee joint. In view of the early motion and the relatively insecure suture of the crucial ligament, no great hope for its functional restoration was held. On April 2 the patient was discharged from the hospital with perfect stability and a normal range of painless motion.

In these cases, as in several others, an observation was made which may be of value in throwing light on the relatively low incidence of positive results in the application of a test a positive reaction to which has been considered pathognomonic of injury to the crucial ligament. In the first place, it was noted that in cases in which the patient gave negative reactions to the test before operation, a "rocker" sign might be obtained when the patient was under anesthesia. At first this was noted with a keen sense of chagrin; it was considered to indicate carelessness in the examination. However, when this phenomenon was observed repeatedly, even after particular attention had been paid to the presence of the sign, it was realized that the anesthetic relaxation of the patient had entirely altered the condition under which the two tests were made. When the tone of the quadriceps and the other muscles which control the action of the knee had been abolished, it was possible to demonstrate excessive anterior mobility of the flexed knee. The prompt disappearance of this sign on the resumption of active motion and the reestablishment of the normal tone of the muscles led to the belief that the quadriceps extensor played an important rôle in the elicitation of the "rocker" sign. In case 3, to be reported, the patient had developed such control over his muscles that he was able voluntarily to project or retract the lower end of the femur on the fixed, flexed leg.

In cases of hypotonia<sup>14</sup> due to repeated effusion in the joint or to dysfunction of the parathyroid mechanism it is known that such relaxation of the muscular and ligamentous structures may occur. The significance of this factor in the evaluation of the rocker sign has been overlooked, though its value in the treatment of the underlying condition

---

14. Finkelstein, H.: Joint Hypotonia, New York M. J. 104:942 (Nov. 11) 1916.

seems to have been amply appreciated. Timbrell Fisher<sup>15</sup> stated that "the most important factor in the treatment is so to build up the quadriceps extensor that they compensate, to a certain extent, for the weakness and instability caused by the loss of the action of the crucial ligament. In at least two cases, in which complete rupture of the anterior crucial was found at operation by the author, attention to this principle has enabled the patients to continue playing strenuous football." For my part, I have been led to feel that this is true only in



Fig. 1.—Anteroposterior roentgenogram showing a sprain fracture of the medial femoral condyle at the insertion of the tibial collateral ligament and a sprain fracture of the medial tibial spine at the insertion of the anterior crucial ligament.

instances in which no associated injury to the internal lateral ligament is found. In such cases, the extension test has invariably been negative, while the "rocker" test has or has not been positive, depending on the degree of tone in the quadriceps muscle. But in cases in which an injury to the internal lateral ligament has been superadded to the injury to the crucial ligament, the reactions to both tests has been found to

15. Fisher, A. G. Timbrell: *Internal Derangements of the Knee Joint*, ed. 2. New York, The Macmillan Company, 1933, p. 171.

be positive, regardless of the power of the quadriceps, and this can be explained only on the basis of the additional injury. Most frequently the word of the examining physician as to the true state of affairs, especially as regards the lateral ligaments, must be accepted without any other affirmation. In one patient who is at present under observation but who has not yet consented to operation it was possible to obtain roentgenographic evidence (fig. 1) of the tearing away of both the crucial ligament and the tibial collateral ligament. The feeling that the major part of the disability in such cases is due to the insufficiency of the lateral ligament has been confirmed by the study of the following cases.

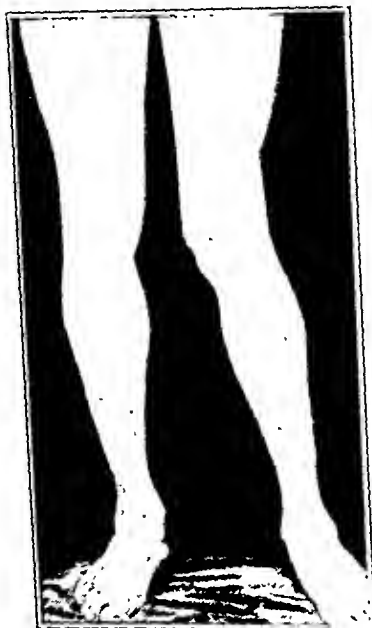


Fig. 2 (case 3).—Photograph showing abduction of the knee, with separation of the medial femoral and tibial condyles, due to rupture of the tibial collateral ligament.

*CASE 3.—Reconstruction of the anterior crucial and internal lateral ligaments by the method of Hey Groves and Smith.*

W. S., a man, aged 26, was admitted to the hospital on Nov. 18, 1929; his left knee had been run over by an automobile one year before. The only treatment had consisted in a two weeks' period of hospitalization in a midwestern institution. Since that time he had noted marked instability in the knee, with a tendency to dislocation on going up or down stairs. There was no history of locking. It was noted that "in spite of the rather serious nature of the injury, the patient is still able to walk fairly comfortably and with a fair degree of stability. This stability is largely maintained by the action of the hamstrings and the quadriceps muscles. When seated, the patient can project the lower end of the femur backward and forward on the tibia and can rotate the femur externally." There was

a typical "rocker" sign with the knee flexed, and with the knee extended, external rotation of the leg, hyperextension of 5 degrees, abnormal backward and forward displacement and abduction of 10 degrees were possible (fig. 2). The roentgenogram showed a "small calcific body, perhaps a detached crucial spine, in the knee joint." A diagnosis of rupture of both crucial ligaments and the tibial collateral ligament was made, and operation was advised.

Arthrotomy, performed on November 21, disclosed absence of the anterior crucial ligament. The stump of the posterior crucial ligament was found in the depression behind the crucial spine. The tibial collateral ligament was torn, and the medial semilunar cartilage was detached. The semilunar cartilage was resected, and a typical Hey Groves-Smith reconstruction was performed, special attention being paid to the repair of the internal lateral ligament. It was noticed on the operating table that when repair of the internal ligament had been completed, practically complete stability of the knee joint was restored. After closure of the wound, a plaster of paris bandage cast was applied, with the knee in extension. On Jan. 27, 1930, the cast was removed, a knee-cage brace was fitted, and active motion was begun. By February 24, extension of the knee to 180 degrees and flexion to 115 degrees were possible. By April 28 flexion had increased to 90 degrees, and the patient could run or hop upstairs, bearing his weight normally on the leg on which operation had been performed. There was no evidence of anteroposterior mobility, but there was a slight degree of lateral mobility, which did not interfere with the function of the knee. Thereafter the patient was lost sight of.

This case is of special interest, because of the presence of injury to the posterior crucial ligament. Since some authors claim that the posterior crucial ligament is of the greatest importance in maintaining the stability of the knee, it would be of great value to be able to determine this point in a case in which repair of this ligament had been purposely neglected. However, the fact that there was a slight degree of lateral instability inclines me to the opinion that the instability was occasioned either by insufficient tension on the fascial graft at the time of the operation or by relaxation of the graft subsequent to the beginning of active motion.

*CASE 4.—Hey Groves reconstruction of the anterior crucial ligament.*

F. L., a man, aged 38, was first seen in May 1930. He was a printing press rigger and in the course of his work had been injured by a piece of machinery which fell on his right side. He was taken in an unconscious condition to a nearby hospital, where a diagnosis of fracture of the pelvis, probable fracture of the ribs and an internal derangement of the right knee was made. He remained at the hospital for about three months. On his discharge he noted swelling of the knee. He returned to his work, but was forced to discontinue it because of recurrent swellings, occasional giving way and a sensation as of something clicking on the inner aspect of the knee.

He walked fairly well but with a marked limp. The knee was distended by fluid, and there was tenderness on pressure over the anterior horn of the internal semilunar cartilage, as well as over the internal lateral ligament. There was no lateral hypermobility, but with the knee in flexion there was a definite "rocker" sign. A tentative diagnosis of fracture of the semilunar cartilage with rupture

of the anterior crucial ligament was made, and operation was recommended. This was undertaken on May 15, through a median parapatellar incision. The anterior crucial ligament was found torn away from its femoral attachment and rolled on itself. The posterior crucial ligament was frayed and attached by only a few fibers. The semilunar cartilage was normal. A Hey Groves operation without the Smith modification, because of the absence of signs of lateral mobility, was carried out. The cartilage was left in situ, and the leg was encased in plaster of paris after closure of the wound. By June 21, on removal of the cast, the patient could passively flex the knee to a right angle. In this position there was no sign of abnormal anteroposterior mobility. A knee-cage brace was applied, and active motion was begun. The patient was discharged from the hospital on July 12, walking, and was thereafter given physical therapy. In September he resumed



Fig. 3 (case 4).—Photograph showing the postoperative state. The patient's ability to bear weight in the partly flexed position, in the act of ascending the stairs, is seen.

his work. However, in October he again returned to me with a swollen knee, and in December there had been a return of the anteroposterior mobility previously noted. He was given rest and physical therapy, with marked improvement. In February 1931, he returned to his usual work and was then lost sight of until June, when he was again examined. At that time there was no lateral mobility and there was still slight anteroposterior mobility, but the musculature had so strengthened that the patient could perform his work, using his knee in a perfectly normal manner (fig. 3).

CASE 5.—*Resection of the anterior crucial ligament and medial semilunar cartilage.*

M. K., a man, aged 31, was seen on Oct. 4, 1933, with a history of having injured the left knee while playing Gaelic football one year previously. He

jumped to catch the ball and landed on his feet, with the left leg abducted and externally rotated and with the thigh adducted. He was unable to extend the leg until some friends "pulled the leg out," when he felt something slip into place. Though he attempted to continue the game, the swelling and pain were so severe that he was forced to desist. He remained in bed for four days, after which the symptoms had so far receded that he thought that he was well, though he admitted that he had a sensation of weakness in going up or down stairs. After several months the patient resumed his playing of football, with exactly similar consequences. Several months after this attack he again attempted to carry on his professional football career, with recurrence of the symptoms. Since this last episode the patient had noticed that whenever he twisted suddenly "something seemed to slip out of place in the left knee," which then became locked in flexion.

Examination disclosed that the patient walked without a limp. There was no fluid in the knee joint, no crepitus on motion and no abnormal mobility, either anteroposteriorly or laterally. There was slight swelling over the postpatellar fat pads, with an obliteration of the parapatellar depressions. There was definite tenderness over the anterior horn of the medial semilunar cartilage, with accentuation of tenderness on extension of the leg. A diagnosis of fracture of the medial semilunar cartilage was made, and operation was advised. Arthrotomy, performed on Nov. 8, 1933, showed a moderate increase in synovial fluid and marked congestion, with thickening of the entire synovial membranes and of the semilunar fat pads. The internal semilunar cartilage was found shrunken. The crescentic free edge was blunted, and its posterior part was torn half through. The anterior crucial ligament was torn away from its femoral attachment, and the free edge was frayed, as if it had been crushed between the femoral and tibial condyles. With the patient under anesthesia a positive "rocker" sign could readily be demonstrated. The cartilage was resected, along with the damaged portion of the postpatellar fat pad. The stump of the crucial ligament was cut away from its tibial insertion, and the wound was closed in the usual manner. The pathologic specimen was reported as showing in the cartilage "a tendency to fibre out," in the shreds of the crucial ligament "a very marked myxoid degeneration, with proliferating cartilage cells in some areas" and in the synovial tissue "villous hypertrophy and round cell infiltration." On the patient's discharge from the hospital he was able to extend the knee completely and to flex it to about 90 degrees. There was no evidence of abnormal mobility either in the anteroposterior or in the lateral direction.

CASE 6.—*Resection of the anterior crucial ligament and medial meniscus.*

P. C., a man, aged 42, was seen on April 3, 1934, with a history of having fallen on the flexed and abducted right knee more than six weeks previously. Immediately after the accident, on attempting to arise, the patient noted a click on the inner aspect of the knee; he was unable to straighten his leg. Within a short time the knee became markedly swollen, and he was forced to discontinue his work. His physician advised hot compresses and diathermy, but there was no relief. Since then the patient had noted locking of the knee at least once daily and a marked sense of insecurity in going up or down stairs. On examination he walked with a definite limp and was unable to bring the heel to the floor because of the flexion at the knee joint. The knee was slightly enlarged, contained a slightly increased amount of fluid and gave a definite patellar ballotement. Extension was possible to 140 degrees and flexion to 90 degrees. There was tenderness over the anterior horn of the medial semilunar cartilage, with accentuation of the tenderness on extension of the leg. A slight degree of abnormal motion

ity could be demonstrated both in the anteroposterior and in the lateral direction. This observation could not be accurately evaluated because the knee could not be brought into full extension. However, a tentative diagnosis of bucket-handle fracture of the semilunar cartilage, with the possibility of an injury to the anterior crucial ligament, was made, and arthrotoomy was advised. The joint was opened through a small vertical median parapatellar incision. A typical bucket-handle fracture of the medial semilunar cartilage was observed, as well as a tearing away of the anterior crucial ligament from its tibial attachment. The cartilage was resected. This permitted complete extension of the knee, when it was observed that there was no lateral mobility. It was consequently believed that the lateral mobility previously observed was apparent and was due to the fact that the knee could not be properly extended. The anterior crucial ligament was thereupon resected, and the knee was closed in the usual manner, without immobilization. Motion was started as soon as the postoperative pain had disappeared. There was no evidence of abnormal anteroposterior mobility. Walking was permitted on the tenth day, just before the patient's discharge from the hospital. Within three weeks of his operation the patient was able to flex the knee beyond a right angle and to extend the leg completely. There was no instability. The patient could use his knee normally, and after an additional period of four weeks of physical therapy he returned to his regular work. Subsequently marked lateral instability of the knee, which was not improved by exercise, support, etc., developed; a Smith repair of the tibial collateral ligament was advised.

*CASE 7.—Smith reconstruction of the internal lateral ligament for rupture of the anterior crucial and the internal lateral ligament.*

B. G., a woman, aged 26, was seen in January 1934, with a history of having fallen on her flexed right knee more than nine years before. After a short period of treatment the swelling and disability disappeared, and the patient was able to resume her usual activities. She noted, however, that when she was swimming her knee occasionally locked and that there was a sense of insecurity in going up or downstairs. In July 1933 she had jumped off a low bulkhead and had landed on her partly flexed knee; she had then fallen backward and twisted the knee. She immediately complained of severe pain and inability to bear her weight, because of giving way of the knee. She was treated conservatively by means of a cast and physical therapy, with some relief, though complete extension of the leg was impossible. Roentgen examination showed no evidence of fracture. There was marked atrophy of the left thigh. There was no fluid in the knee joint or crepitus on motion. Extension was possible to about 175 degrees. Flexion was normal. In extension there was a slight degree of abnormal adductibility. In flexion the tibia could be displaced forward on the femur. There was definite tenderness over the tibial insertion of the tibial collateral ligament, and slight tenderness was noted over the anterior horn of the medial meniscus, with accentuation of the pain on extension. It was felt that the patient was suffering from a lesion of the medial meniscus and a relaxation of the internal lateral ligament, with possibly a tear of the anterior crucial ligament. Operation was suggested.

The patient entered the hospital on February 5, and arthrotoomy was performed several days later. With the patient under anesthesia, it was remarked that with the leg both in flexion and in extension there was marked lateral, as well as anteroposterior, mobility. When the joint was opened, the medial meniscus was found to be loose. There was an erosion of the cartilage on the inferior surface of the medial femoral condyle. The anterior crucial ligament was diligently sought for, but it could not be found. It was readily seen that the posterior crucial ligament



was normal. The cartilage was resected. Two tunnels were then drilled in the coronal plane through the lower end of the femur and the upper end of the tibia. A long strip of fascia lata was freed subcutaneously, being left attached at its lower end. The upper end of the fascial graft was then passed through the femoral bone tunnel from without inward and was sutured to the periosteum both at its entrance and at its exit from the bone. It was then passed down the inner aspect of the knee in the plane of the anterior portion of the medial collateral ligament and with the leg in slight forced adduction was passed through the tibial tunnel from within outward, being again sutured to the periosteum at both extremities of the tunnel. Immediately after completion of this step of the operation it was observed that lateral stability had been completely restored but that anteroposterior mobility persisted. The wounds were closed, and a plaster of paris bandage cast was applied from the toes to the mid thigh, with the knee in slight flexion. The leg was not dressed until March 28, at which time the wounds were found to be healed. There was moderate swelling of the knee, as was to be expected. Lateral motion was present in slight degree. About 20 degrees of active motion was possible. Under treatment with physical therapy, active and passive motion and the application of diathermia to the knee and sinusoidal current to the quadriceps muscle, the instability gradually disappeared, and the range of normal motion gradually increased, until by the middle of May extension to 180 degrees and flexion to 90 degrees were possible, without any evidence of either anteroposterior or lateral mobility.

The importance of the internal lateral ligament in maintaining the integrity of the knee joint is well attested by the following case.

*CASE 8.—Rupture of the anterior crucial and fibular collateral ligaments.*

Dr. M. F., a man, aged 24, was seen in July 1932. He had injured the knee one week previously. While he was wrestling on the beach, one of his comrades had fallen on top of the extended right knee and hyperextended it to the point at which a forward dislocation of the tibia on the femur had occurred. With some difficulty his friends reduced the dislocation by traction and the patient was taken home. At the time of the first examination the knee was still markedly swollen. The skin was ecchymotic well down in the leg, and there was a marked effusion into the articular space. The knee could be extended to 180 degrees and flexed to 90 degrees. In the flexed position there was slight anteroposterior motion, and in the extended position hyperadduction of about 15 degrees was possible. The internal ligament appeared to be intact. The roentgenogram showed a shadow suggestive of a sprain fracture of the medial tibial condyle. There was no interference with the circulation of the leg or evidence of injury to the posterior tibial or peroneal nerves.

It was considered that the patient had suffered a rupture of the posterior portion of the capsule, with a tear of the anterior crucial and fibular collateral ligaments. But in view of the fact that the internal lateral ligament was apparently not involved, it was felt that immobilization was unnecessary. A knee-cage brace was fitted, the outer border of the sole and heel of the shoe was elevated, and the patient was encouraged to make gentle, active use of the knee. Diathermia was begun as soon as the patient was able. After about six months, as soon as complete stability of the knee had returned, the knee-cage brace was discarded, and at the present time (1934) the patient is able to engage normally in sports without any trace of inconvenience. There is no weakness, and there is no suggestion of anteroposterior or lateral hypermobility in either the flexed or the extended position.

## COMMENT

Though the opinions expressed here were arrived at independently, it must be admitted that they were held with great temerity until reference to the literature discovered that other surgeons had given utterance to the same beliefs at an earlier date and with much more assurance. Le Riche,<sup>16</sup> who resected the anterior crucial ligament with perfect functional result, is reported to have observed that "excision of the anterior crucial ligament is compatible with functional restoration of the joint and is always satisfactory." Tixier and de Rougemont,<sup>17</sup> in discussing the question of diagnosis, stated: "One must say the diagnosis of a lesion of the crucial ligaments is often impossible, but of secondary importance, while it is vital to determine especially a lesion of the lateral ligament." In considering the matter of therapy they said: "We consider that the repair of the crucial does not constitute the indispensable element of success. . . . There is one essential step; the repair of the lateral." Tavernier,<sup>18</sup> who was of the same opinion, wrote: "I am constrained to suppose that the laxity presupposes rupture of ligaments other than the anterior crucial—possibly especially certain of the deep fibres of the internal lateral ligament." In 1932 he<sup>19</sup> reported a case in which both crucial ligaments and the internal lateral ligament were torn and in which repair of the latter ligament alone led to the restoration of a thoroughly stable, normally functioning knee joint.

As a conclusion from these and the previously noted considerations, I have come to believe that, contrary to the general opinion, the anterior crucial ligament is not a vitally necessary structure and that its loss is thoroughly compatible with relatively normal function of the knee, that the diagnosis of rupture of this ligament alone is not as simple as it has been stated to be, that the tests which are reputed to reveal ruptures of the crucial ligament are in all probability indicative of injuries to both the crucial and the internal lateral ligament, that the disability is due primarily to the loss of integrity of the internal lateral ligament and that in consequence surgical efforts should be directed primarily toward the repair of the internal lateral ligament by means of the Alwyn Smith operation rather than to the repair of the crucial ligament by means of the Hey Groves procedure.

2178 Broadway.

16. Le Riche, R.: *Lyon chir.* **16**:461, 1916; *J. de chir.* **34**:1, 1929.

17. Tixier, L., and de Rougemont, J.: *Rev. de chir.*, Paris **51**:589 (Oct.) 1932.

18. Tavernier, L.: *Lyon chir.* **16**:353, 1919.

19. Tavernier, L.: *Lyon chir.* **29**:610, 1932.

# LYMPHOGRANULOMA INGUINALE

ITS RELATION TO STRICTURE OF THE RECTUM

WARREN RAINEY, M.D.

AND

WARREN H. COLE, M.D.

ST. LOUIS

Although lymphogranuloma inguinale has been recognized by the medical profession in some form or other under various names for several decades and the pathogenesis as well as other features were carefully described by Durand, Nicolas and Favre<sup>1</sup> in 1913, it has been only during the past year or two that the American literature has contained any significant references to it. DeWolf and Van Cleve<sup>2</sup> were probably the first American authors to report observations on the disease. When one considers the number of cases described in various reports, lymphogranuloma is apparently rather common. During the year that we have devoted attention to the disease in the clinic of Washington University we have encountered twenty-three cases. Innumerable synonymous terms, such as tropical bubo, climatic bubo and venereal lymphadenitis, have been used to identify the disease. If any of them is superior to lymphogranuloma inguinale, the term venereal lymphogranuloma appears to be most applicable. Ives and Katz,<sup>3</sup> who reported the first case identified in St. Louis, called attention to the vast number of terms which have been attached to the disease.

## PATHOGENESIS

The etiologic factor in the production of the disease is probably a virus which gains entrance through a tiny or unnoticed primary lesion on the genitals and is no doubt dependent on sexual contact for transmission. The incubation time as given by numerous observers is from ten days to three weeks, although in one of our cases it was definitely

---

From the Department of Surgery, Washington University School of Medicine, the Washington University Clinics and Barnes Hospital.

1. Durand, M.; Nicolas, J., and Favre, M.: *Lymphogranuloma inguinale subaigu d'origine g nitale probable, peut tre v n rienne*. Bull. et m m. Soc. m d. d. h p. de Paris **35**:274, 1913.

2. DeWolf, H. F., and Van Cleve, J. V.: *Lymphogranuloma Inguinale*, J. A. M. A. **99**:1065 (Sept. 24) 1932.

3. Ives, George, and Katz, S. D.: *Lymphogranuloma Inguinale, with Report of a Case*, Weekly Bull. St. Louis M. Soc. **27**:197, 1932.

proved to be five weeks. The primary lesion is so small that it is seldom noticed by the patient. When visible it is a tiny ulcer or fissure. However, in one of our female patients as many as eight or ten tiny superficial ulcers were visible on all sides of the vagina near the outlet at the time of her initial visit, which was three weeks after the onset of swelling of the inguinal lymph nodes. The disease, in this country at least, is more common in the Negro race. In our series of twenty-three cases, 87 per cent of the patients were Negroes. An observation which has been universally noted is the tendency toward the production of inguinal adenitis in men and the production of rectal ulceration or strictures in women. Weiss,<sup>4</sup> of Strashourg, is conducting an extensive study and survey of the disease, devoting particular attention to the relation of the disease to benign stricture of the rectum. Symptoms indicative of stricture may not be noted by the patient for six or eight years following the initial symptoms. The rectal lesion is more apt to be followed by stricture in Negro women than in men or in white women. The explanation of the tendency toward involvement of the lymph nodes in men and of the rectum in women has been discussed in detail by Barthels and Biberstein,<sup>5</sup> Jersild<sup>6</sup> and Semba<sup>7</sup> and has been reviewed recently by Bloom.<sup>8</sup> In men most of the lymphatics from the penis, where the primary lesion is most apt to occur, drain anteriorly into the lymph nodes of the groins. On the contrary, most of the lymphatics of the vagina, especially of the proximal and posterior portion of the vagina, drain posteriorly into the lymph nodes along the rectum. Because it is so difficult to demonstrate a prominent enlargement or involvement of these nodes, there is still some difficulty in explaining the pathogenesis of the rectal lesions. It is possible that as the lymph nodes along the rectum become involved the stasis of the lymphatic system in the rectal wall distal to the nodes produces edema which encourages invasion by the virus and possible secondary invasion by organisms. The tendency toward the production of excessive scar formation following injury or infection in the Negro may explain the

4. Weiss, A. G.: Personal communication to the authors.

5. Barthels, C., and Biberstein, H.: Elephantiasis penis et scroti und Lymphogranulomatosis inguinalis, *Beitr. z. klin. Chir.* **152**:325, 1931.

6. Jersild, O.: Notice historique sur l'infiltration hyperplásique du rectum avec rétrécissement fibreux et sur l'origine prétendue syphilitique de cette affection, *Ann. de dermat. et syph.* **7**:74, 1926; Elephantiasis genito-anorectatis, *Dermat. Wehnschr.* **96**:433, 1933.

7. Semba, Y.: Anatomische Untersuchungen über die Lymphgefäßsysteme des Rektum, mit besonderer Berücksichtigung der Metastasenbildung des Rektumkrebses, *Arch. f. klin. Chir.* **149**:336, 1928.

8. Bloom, D.: Strictures of the Rectum Due to Lymphogranuloma Inguinale, *Surg., Gynec. & Obst.* **58**:827, 1934.

greater incidence of stricture in Negro women as compared with white women. It is thought by some that contamination of the rectum from the infected discharge of the vagina may account for the involvement of the rectum. It would, however, be difficult to explain involvement of the rectum in man, which is occasionally noted, unless homosexuality is a factor. Sexual perversion and homosexuality have been emphasized by some (Coultz and his associates<sup>9</sup>) as an important factor in the production of the disease in the rectum.

Various experiments have been resorted to in an effort to reproduce the disease, and it is significant that experimental transmission is perhaps more readily accomplished than in any other disease known. The reports of these experiments have recently been reviewed in the thorough and valuable report by H. N. Cole<sup>10</sup> and will not be discussed here. The disease has been successfully transmitted to white mice, guinea-pigs, rabbits, monkeys and man. Levaditi and his associates<sup>11</sup> have done or confirmed a great portion of the work on the transmission of the virus.

Attention should be called to the fact that absolute proof of the causation of benign stricture is still lacking, although all observers who have devoted any attention to this phase of the disease are convinced that the greater portion (perhaps 90 per cent or more) of benign strictures of the rectum are due to lymphogranuloma inguinale. The positive Frei test obtained in association with these strictures is probably the most reliable evidence that rectal stricture is a part of the disease. However, we have observed at least one patient (no. 8, table 3) in whom a stricture of the rectum developed when only edema and ulceration were observed on the first examination. In this instance rectal symptoms, including chiefly tenesmus and the occurrence of blood and pus in the stool, were first noted by the patient in 1927. In 1931, when first seen by us, she had ulceration and edema of the rectum without narrowing of the lumen. One year later it was noted that a stricture was forming, and in 1934 the scar tissue was densely deposited on all sides of the rectum so that it barely admitted the tip of the index finger.

The fact that the Frei test is positive in these cases of rectal stricture added to the observation just noted convinces us that rectal stricture is

---

9. Coultz, W. E.; Herrera, J. M., and Perroni, F. L.: *Lymphogranulomatosis Venerea*, Am. J. Surg. **21**:96, 1933.

10. Cole, H. N.: *Lymphogranuloma Inguinale, the Fourth Venereal Disease*, J. A. M. A. **101**:1069 (Sept. 30) 1933.

11. Levaditi, C.; Ravaut, P., and Schoen, R.: *Propriétés virulicides du sérum des sujets atteints de lymphogranulomatose inguinale*, Compt. rend. Soc. de biol. **109**:1267, 1932.

a part of the disease. In our hands the Frei test<sup>12</sup> has been remarkably specific. Every patient in our series who exhibited a positive Frei reaction was afflicted with one of the three major manifestations, namely, inguinal adenitis, ulcerative proctitis or rectal stricture.

The antigen is made by aspirating pus under sterile precautions from the groin of a person known to have the disease and diluting the pus with sterile physiologic solution of sodium chloride in a proportion of 1 to 4 or 1 to 2 depending on the thickness of the pus. It is sterilized by heating in a water bath at 60 C. for two hours one day and heating at 60 C. for an hour a day or two later. Obviously if culture of the antigen reveals bacterial growth false positive reactions will be obtained. The dose is 0.1 cc. intradermally. The typical reaction is an induration at the site of the injection which is at its maximum in forty-eight hours and may measure from 1 to 2 cm. in diameter. This area may be tender and is usually surrounded by an areola of redness. The test should be positive after the disease has been present for ten days or more, and in our experience the test remains positive as long as twelve to fifteen years after the onset of the disease. Usually, however, patients with an acute form give a stronger reaction. If when the disease is strongly suspected a negative or doubtful reaction is obtained, the test should be repeated. The incidence of a positive Wassermann or Kahn reaction in patients with rectal stricture, as noted in table 1 (28.5 per cent), seems entirely too small to admit the possibility of syphilis as being an important factor in the cause of stricture of the rectum. This incidence is no greater than the incidence noted in any other group of patients of the same social status. Of the fifteen patients with rectal stricture observed in our clinic during the past year, all except one gave a positive reaction to the Frei test. The patient with the negative reaction had a condition which had been diagnosed as one of the rare instances of rectal stricture occurring with idiopathic colitis. The extent of involvement of the colon in this case offered a contrast to the confinement of the disease to the terminal portion in lymphogranuloma inguinale. We conducted Frei tests on numerous patients with variable diagnoses, including syphilis, tuberculosis of the inguinal and cervical lymph nodes, granuloma inguinale and fistula in ano, but in every instance the reaction was negative. The fact that every one of these tests was negative is perhaps accidental, because in another series one might expect to encounter patients (especially men) who had had lymphogranuloma inguinale but recovered without residual symptoms.

12. Frei, W.: Eine neue Hautreaktion bei Lymphogranuloma inguinale, *Klin. Wchnschr.* 42:2148, 1925.

Attention should be called to the fact that numerous observers have reported false positive Wassermann or Kahn reactions in cases of lymphogranuloma inguinale. We have one patient under observation a woman (patient 19, table 3) with definite evidence of acute lymphogranuloma inguinale whose reaction to the Kahn test was positive and remained so after thorough antisyphilitic treatment. The fact that she is young (26 years) seems to minimize the possibility that she has "Kahn-fast syphilis."

#### CLINICAL MANIFESTATIONS

In men the development of inguinal adenitis occurs in practically every instance. The swelling is usually bilateral and begins insidiously (the primary lesion is rarely observed by the patient) from ten days to



Fig. 1.—A Negro man with involvement of the inguinal lymph nodes on each side. The sinus present on the right was recent (of two or three weeks' duration) and resulted from the rupture of a small abscess of a lymph node to the exterior.

five weeks following exposure. Tenderness and pain are usually absent at first but may be present several weeks after the nodes become involved. Formation of an abscess with fluctuation usually occurs, but the amount of time required for its development is variable. Once fluctuation develops the abscess invariably breaks through the skin unless the pus is evacuated by incision or aspiration. In one of our cases aspiration of an abscess of an inguinal lymph node resulted in a cure as far as the local lesion was concerned. On rare occasions the suppuration of the nodes may subside and the sinuses close from six to eight weeks after the onset of swelling. As a rule, however, the sinuses and enlargement of the lymph nodes persist for many months. Ulcerative proctitis, which occurs in probably more than 75 per cent

of the women but in not more than 25 per cent of the men, may also be insidious in its development, although the presence of blood, pus and mucus in the stool is almost always detected by observing the patient shortly after the onset. Tenesmus and diarrhea may be present, although constipation may be very annoying when the formation of the stricture begins. Obviously, after the stricture becomes pronounced a loose watery stool is the only kind that the patient can pass. Multiple fistulas are not uncommon. Various types of condylomatous and granulomatous masses are observed about the anus. Sinus tracts and scarring about the vulva and anus are likewise commonly reported, but they were not seen frequently in our series.

As previously stated, when inguinal adenitis is the only manifestation of the disease there is rarely any permanent damage. Figures are not available as to the incidence of stricture following ulcerative proctitis, but the incidence is probably extremely high in Negro women if the disease is untreated, but low in men. On a few occasions ulcerative proctitis has been known to develop years after involvement of the inguinal lymph nodes, although it is probable that the disease had existed in the rectum in a very mild form since the initial symptoms. Likewise, ulcerative proctitis may exist for years before a stricture develops. In one patient under our observation the ulceration in the rectum was known to exist for five years before a stricture formed.

We wish to emphasize the occurrence and severity of the systemic reaction which is seen only occasionally in men but in the greater majority of Negro women. In such instances the disease is devastating, causing invalidism for years and acting occasionally as a secondary cause of death. In our series scarcely half the Negro women sustained a systemic reaction according to our records, but we are inclined to believe that the majority of them do have a systemic reaction since the patients who gave no history of such a reaction were patients who had had the disease for many years, but, being of an unobserving class, had no doubt forgotten or misinterpreted the symptoms. In many cases in Negro women the first symptom complained of is diffuse abdominal cramps. A temperature as high as 39 C. (102.2 F.) is not uncommon. Anorexia is prominent and persistent and is accompanied by a sharp loss of weight. Nausea and vomiting are uncommon but may occur. Extreme malaise and weakness may be present. Diffuse pains in the joints with occasional swelling and apparent deformity may be encountered and are one of the features which make a hopeless invalid of the patient. Any of these symptoms may remain for years unless relieved by treatment with antimony and potassium tartrate.

The appearance of the lesion in the rectum is fairly characteristic. In the early stages, when ulcerative proctitis is present without narrowing of the lumen, the mucosa is edematous, thickened and studded here



and there with tiny ulcers which appear superficial. This proctitis is limited almost invariably to an area from 1 to 6 inches (2.5 to 15 cm.) above the anal margin. Above this area the mucosa is normal. A moderate amount of blood and pus may be seen in the lumen, and their presence in the stool may be one of the first symptoms noted by the patient.

The formation of a stricture, which in our experience occurs in a far greater percentage of cases in the Negro than in the white race, occurs at the site of the proctitis just noted. Digital examination of the rectum in over two hundred Negro women with benign stricture of the rectum, during the last fifteen years, disclosed that in nearly every case the upper limits of the growth can be reached with the examining finger if the lumen of the stricture permits the finger to pass. The mucosa in the upper portion of the rectum and sigmoid flexure is invariably normal. The mucosa just above the point of the stricture may show varying degrees of thickening and infiltration which increases or diminishes according to the constriction of the stricture. The sense of firmness and smooth nodular infiltration is so characteristic in a Negro that carcinoma scarcely need be considered in the differential diagnosis.

In a vast majority of patients the site of the stricture is within 5 cm. of the mucocutaneous line. The involvement does not extend into the anus proper, but a secondary infiltration of the surrounding skin tabs is present. This is presumably due to secondary stasis and chronic inflammation resulting from the persistent discharge from the rectum. We have seen rather large and painful masses about the anal margin disappear under treatment with antimony and potassium tartrate. The mucosa of the rectum external to the stricture is invariably infiltrated and ulcerated.

Single or multiple fistulas may develop in an early stage of the disease. The internal opening is above the stricture and when the constriction becomes complete conducts the fecal current out through the single or many discharging sinuses located about the rectum.

#### DIFFERENTIAL DIAGNOSIS

The disease, if stricture of the rectum is admitted to be part of the picture, is characteristic and should not be confused with any other disease except perhaps chancroidal bubo and tuberculosis of the inguinal lymph nodes. Culture of the pus obtained from the groin reveals no growth. It appears, however, that tuberculosis of the inguinal lymph nodes is rare, and many cases of lymphogranuloma inguinale have erroneously been diagnosed as such in the past. Injection of tuberculous pus into a guinea-pig will, of course, produce tuberculous lesions. Microscopically the lymph nodes resemble tuberculosis in that there is

evidence of chronic inflammation in each with accompanying giant cells. If a lymph node is excised in the acute stage, section should show tiny yellowish abscesses which on microscopic examination with the ordinary stains is seen as a necrotic mass resembling caseation which is surrounded by a palisade of epithelioid cells (fig. 2). This area of necrosis may be round but frequently is star-shaped. When present to a marked degree this palisading of epithelioid cells is so characteristic that the diagnosis is practically certain. In tuberculosis one occasionally sees the epithelioid cells around a tubercle arrange themselves in this fashion.



Fig. 2.—A low power photomicrograph of a tiny abscess of a suppurating lymph node from the patient shown in figure 1. Note the caseous center with the palisade of epithelioid cells at the periphery. These abscesses may be star-shaped instead of round and are characteristic of the disease, provided the lymph node is removed before the suppurative process has healed.

but never have we seen such a typical arrangement as is found in lymphogranuloma inguinale. Unfortunately the node must be in the proper stage of suppuration or the lesion will be indistinguishable from tuberculosis. In this case the Frei test should, however, clarify the diagnosis. Except on rare occasions a chancroidal bubo is accompanied or immediately preceded by an extensive ulceration about the genitals, which is never present in lymphogranuloma as a primary

lesion. The disease should not be confused with granuloma inguinale, which does not affect the lymph nodes but manifests itself as a granulomatous ulceration of the genital region which on certain occasions may be present in the groin. Antimony and potassium tartrate is a specific in the treatment of granuloma inguinale but is only moderately beneficial as a therapeutic agent in the treatment of lymphogranuloma inguinale. Lymphogranuloma should not be confused with syphilis, since the lymph nodes in the latter disease have no evident inflammation about them and never suppurate unless complicated by a secondary disease. Moreover, in our experience, inguinal adenitis secondary to a syphilitic ulcer about the anus or perineum usually is unilateral and should, of course, respond to treatment with arsphenamine. We wish to repeat that with a satisfactory antigen the Frei test is extremely reliable and in our hands has been very helpful. Obviously, if the antigen is obtained from a patient who previously had chancroidal disease, a false positive reaction might be obtained. Moreover, in a patient who has had lymphogranuloma years previously, a positive reaction will develop when the active lesion is in reality caused by an entirely different disease. Such pitfalls must be kept in mind, because in a large series such sources of error will be encountered.

#### TREATMENT

When the disease is confined to inguinal adenitis the treatment need not vary much from the treatment of any subacute or chronic inflammation. When pus accumulates it may be evacuated by incision or aspiration. In one of our cases aspiration resulted in a local cure. If sinus formation and enlarged glands in the groin persist for weeks and months the inguinal lymph chain may be excised with a resulting cure of the local process, which may shorten the period during which dressings are needed.

Antimony and potassium tartrate, from 5 to 7 cc. of a 1 per cent solution twice a week for from twelve to fifteen doses, as recommended by many, has been mildly successful in our hands. Two of the patients to whom we gave this were relieved of severe abdominal pain and cramps, which were a part of their systemic reaction to the disease. A large granulomatous and papillomatous mass about the anus of another patient decreased sharply with this treatment. As would be expected the antimony and potassium tartrate did not exert any influence on the rectal stricture. We wish to issue a warning, however, relative to the toxicity of the drug. On several occasions the injection of 5 cc. of a 1 per cent solution produced tachycardia, weak pulse, nausea and vomiting which definitely were not of psychic origin. In another instance after one of the patients had had ten doses of 5 cc. of a 1 per cent solution at semiweekly intervals she awoke one morning with

severe weakness of practically all the muscles in one lower extremity. When seen several days later the weakness was still present but not so prominent. The patient later regained her normal muscle power.

#### ANALYSIS OF CASES

Reference to tables 1, 2 and 3 will obviate the necessity of a detailed discussion of our cases. As can be seen in table 1, only 28.5 per cent of the patients with stricture of the rectum and 33.3 per cent of the patients without stricture of the rectum had a positive Wassermann or

TABLE 1.—*Relation of Lymphogranuloma Inguinale to Syphilis on the Basis of Positive or Negative Wassermann or Kahn Tests*

	Number of Patients	Wassermann or Kahn Test			
		Positive		Negative	
		Number	Per Cent	Number	Per Cent
With stricture.....	14*	4	28.5	10	71.5
Without stricture (inginal adenitis, proctitis).....	9	3	33.3	6	66.6

\* These patients were Negro women.

TABLE 2.—*Clinical Manifestations of Lymphogranuloma Inguinale in Twenty-Three Patients*

	Men	Women
White.....	1	2
Negro.....	2	17
Adenitis.....	4	5 (3 supp.)
Ulcerative proctitis.....	1	5
Stricture.....	0	14
Anal lesions.....	1	3
Rectal fistulas.....	0	2
Systemic reaction.....	0	7*

\* Systemic reaction was evidenced by malaise, anemia, loss of weight, vertigo, abdominal pain, nausea, fever, vomiting and arthritis.

Kahn reaction. Antisyphilitic treatment was given to a number of the patients with rectal stricture (some of whom had a positive Kahn reaction), and in no instance did we observe any favorable results from the therapy. In the group of patients with a positive Kahn reaction are included one or two patients whose reaction was negative when they were seen by us but who had a definite history of syphilis followed by a course of treatment. This percentage of 28 and 33 is no greater than that which might be expected in any group of patients of the same social status. The frequency of occurrence of the various symptoms and signs are given in table 2 and are discussed in the section on clinical manifestations.

TABLE 3.—*Protocol of Cases*

Patient	Age	Sex	Race	Wassermann		Inguinal Lymphadenitis	Rectal Involvement		Additional Data
				or Kahn Test	Frel Test		Ulceration	Stricture	
1. M. B.	25	F	N	— (1+)	++++	No	Blood and pus in stool for a year; ulcerated and edematous mucosa; multiple large external tabs	No, but slight narrowing	Arthritis; loss of weight and strength for 6 months; marked improvement with antimony and potassium tartrate
2. P. W.	27	F	N	—	+++	No	Blood and pus in stool for 2 years; pain; edematous and ulcerated mucosa; large external tabs	No	Improvement with antimony and potassium tartrate; abdominal pain relieved
3. L. B.	28	F	N	—	.....	No	For 3 weeks	No	Abdominal pain most significant symptom
4. F. H.	61	M	W	—	++++	Began on left side 8 weeks before; suppuration 6 weeks before	No	No	Gulnea-plg inoculated with pus from groin gave negative reaction for tuberculous
5. B. M.	20	M	N	—	+++	Swelling in each groin began 1 year before; suppuration 2 weeks later; healed in 3 weeks	Ulcerated mass 2 by 3 cm. on anal margin developed 9 months before; slight edema and ulceration of mucosa	No, but slight narrowing	
6. L. J.	20	M	N	—	+++	Swelling in left groin began 6 months before; nodes above and below inguinal ligament with more below	No	No	Sinus of unexplained etiology in midportion of thigh
7. J. W.	26	F	W	—	++++	No; a few enlarged nodes not noticed by patient	Operation for fistula 5 years before; blood and pus in stool since then	Yes, of at least 2 years' duration	Fever, arthritis and malaise for preceding 3 months; no antisyphilitic treatment
8. E. H.	37	F	N	—	2/1/34 ++++ 3/4/34 ++++	No	Blood and pus first noticed in stool 7 years before; edema and ulceration of mucosa for next 4 years	Yes, of 3 years' duration; barium sulphate enema revealed narrowing as high as sigmoid flexure	No antisyphilitic treatment; no stricture when first seen, in 1931
9. R. S.	38	F	N	—	+++	No	Healed, but stricture present	History suggests 25 years' duration	No antisyphilitic treatment
10. M. G.	34	F	N	—	++	No	Blood and pus in stool 7 years before; ulcerated and edematous mucosa	Of 5 years' duration	No antisyphilitic treatment; stricture just beginning when first seen 7 years before (1927)

[illegible]

## SUMMARY

During the past year we have observed twenty-three cases in which we were convinced that the condition could correctly be classified as lymphogranuloma inguinale. The Frei test was positive in the entire group in which there appeared all three of the major manifestations of the disease, namely, inguinal adenitis, ulcerative proctitis and rectal stricture. On one occasion, however, the reaction to the Frei test was doubtfully positive, but a repetition of the test revealed a strongly positive reaction. The test was made on numerous patients with other diseases, such as syphilis, tuberculosis of the inguinal lymph nodes, stricture of the rectum accompanying obviously idiopathic ulcerative colitis (one case) and other diseases, but was negative in all instances. The disease is mild in men, consisting chiefly of suppurative inguinal adenitis which leaves no residual disease or disability after it heals. The most serious manifestations are encountered in Negro women, in which group systemic reactions are most common and rectal strictures occur. We are of the opinion that the greater portion of the benign rectal strictures so commonly observed in Negro women are due to lymphogranuloma. We observed one patient who had ulcerative proctitis of the type included in our group of cases in whom there developed a stricture of the rectum which was the same type as the strictures reported in this series. The fact that the Frei test was positive in these cases lent support to the probability that lymphogranuloma was the etiologic factor. The incidence of a positive Kahn test of 28.5 per cent in our series of patients with stricture of the rectum appears too small to suggest the possibility of syphilis being the cause. Antimony and potassium tartrate, although not a specific, causes improvement in the acute cases but does not appear to influence favorably the rectal strictures.

NOTE.—Since this article was prepared for publication eighteen additional cases have been observed. The incidence of a positive Wassermann or Kahn reaction in the combined series of patients with stricture of the rectum is not changed appreciably.

# COMBINED AND SEPARATE EFFECTS OF BILE, PANCREATIC SECRETION AND TRAUMA IN EXPERIMENTAL PEPTIC ULCER

AMOS M. GRAVES, M.D.

SAN ANTONIO, TEXAS

Nonhealing peptic ulcers simulating those occurring in man were rarely obtained by any experimental method until Mann<sup>1</sup> in 1923 demonstrated that they could be produced at will in dogs subjected to "duodenal drainage." Later Morton,<sup>2</sup> McCann,<sup>3</sup> Dragstedt,<sup>4</sup> Matthews and Dragstedt,<sup>5</sup> and Weiss and Gurriaran<sup>6</sup> produced similar ulcers in 100 per cent of dogs operated on in the same manner. The peptic ulcers so obtained occurred in the total absence of alkaline pancreatic juice, bile and duodenal secretions, which had been deviated into the lower intestinal tract. While the aforementioned authors conceded that the action of unneutralized acid is an important factor in the production of ulcers, McCann believed that his experiments showed that trauma was an equally, if not more important, factor in the causation of the ulcers obtained by him. The present investigation was undertaken in an attempt to determine the relative effects of unneutralized acid gastric chyme and trauma in the production of experimental peptic ulcer in dogs.

Early investigators studied the effect of acid on gastric mucous membrane of dogs by administering relatively large doses of dilute hydro-

---

This study was aided by a grant from the Schwartz Research Fund.

From the Department of Surgery, School of Medicine, Tulane University of Louisiana.

The article is an abridgement of a thesis submitted to the Faculty of the Graduate School in partial fulfilment for the degree of Doctor of Philosophy.

1. Mann, F. C.: Experimental Production of Peptic Ulcer, *Ann. Surg.* **77**: 409, 1922.

2. Morton, C. B.: Observations on Peptic Ulcer, *Ann. Surg.* **85**:207 and 879, 1927; **87**:401, 1928.

3. McCann, J. C.: Control of Acidity, *Am. J. Physiol.* **89**:483, 1929; Experimental Peptic Ulcer, *Arch. Surg.* **19**:600 (Oct.) 1929.

4. Dragstedt, L. R.: Contributions to the Physiology of the Stomach: XXXVIII. Gastric Juice in Duodenal and Gastric Ulcers, *J. A. M. A.* **68**:330 (Feb. 3) 1917.

5. Matthews, W. B., and Dragstedt, L. R.: The Etiology of Gastric and Duodenal Ulcer, *Surg., Gynec. & Obst.* **55**:265, 1932.

6. Weiss, A. G., and Gurriaran, G.: Ulcères chroniques gastro-duodénaux expérimentaux créés par la dérivation des sucs alcalins duodénaux, *Bull. et mém. Soc. nat. de chir.* **36**:6, 1930.



chloric acid. Erosions and hemorrhagic spots were inconsistently obtained in inverse proportion to the amount of food allowed during the experimental period. This method has recently been revived and has again proved unsatisfactory. However, if gastric acidity is altered by unphysiologic operative methods, chronic ulcers not infrequently occur.

Friedman<sup>7</sup> found that ulcers in the pyloric region produced by submucous injection of silver nitrate became chronic when associated with hyperacidity resulting from pyloric stenosis. O'Shaughnessy,<sup>8</sup> after transplanting patches of jejunal mucosa into the wall of the stomach, performed a gastro-enterostomy "en Y" with occlusion of the pylorus. Following this procedure ulcers occurred in the transplants. Dott and Lim<sup>9</sup> reported that in most instances marginal ulcers formed after the establishment of an experimental gastro-enterostomy whenever the pylorus was occluded. This finding was in agreement with the clinical experience of von Haberer,<sup>10</sup> who observed that jejunal ulcers developed in 12 of 71 patients in whom he performed combined gastro-enterostomy and pyloric occlusion, whereas ulcers developed in only 3 of 275 patients without occlusion. That pyloric occlusion favors a high gastric acidity has been shown experimentally. Friedman and Hamburger<sup>11</sup> found an increase in gastric acidity after narrowing the pylorus with a purse-string suture; defects which they produced in the gastric mucosa failed to heal and frequently developed into peptic ulcers. Bolton<sup>12</sup> also showed that experimentally produced ulcers healed more slowly if the pylorus was constricted by rubber bands. Similar delay in healing was reported by Ivy.<sup>13</sup> That experimentally produced gastric ulcers healed more rapidly when the pylorus was splinted was shown

---

7. Friedman, G. A.: The Influence of Removal of the Adrenals and One-Sided Thyroidectomy upon the Gastric and Duodenal Mucosa: The Experimental Production of Lesions, Erosions, and Acute Ulcer, *J. M. Research* **32**:287, 1913.

8. O'Shaughnessy, L.: Etiology of Peptic Ulcer, *Lancet* **1**:177, 1931.

9. Dott, D. M., and Lim, R. K. S.: Experimental Jejunal Ulcer, *Quart. J. Exper. Physiol.*, supp. 11, 1923, p. 109.

10. von Haberer, H.: Gastric, Duodenal and Peptic Ulcer, *Deutsche Ztschr. f. Chir.* **172**:1, 1922.

11. Friedman, J. C., and Hamburger, W. W.: Experimental Chronic Gastric Ulcer, *J. A. M. A.* **63**:380 (Aug. 1) 1914.

12. Bolton, Charles: Ulcer of the Stomach, London, Edward Arnold & Co., 1913; Further Observation on the Pathology of Gastric Ulcer, *Proc. Roy. Soc., London*, s. B **82**:233, 1910.

13. Ivy, A. C.: Studies on the Experimental Gastric and Duodenal Ulcer, *Am. J. Physiol.* **49**:143, 1919-1920; Contributions to the Physiology of the Stomach: LII. Studies on Gastric Ulcer, *Arch. Int. Med.* **25**:6 (Jan.) 1920; Studies on Gastric and Duodenal Ulcer, *J. A. M. A.* **75**:1540 (Dec. 4) 1920; Secretion Pars Pylorica, *Am. J. Physiol.* **57**:51, 1921.

by Hughson;<sup>14</sup> and Elman and Rowlette<sup>15</sup> demonstrated that division of the pyloric sphincter permitted rapid neutralization of gastric acid.

Bickel,<sup>16</sup> in 1909, obtained a perforating jejunal ulcer by closing the pylorus, performing a gastro-enterostomy and creating external biliary and pancreatic fistulas. He promptly recognized that the presence of bile and pancreatic juice in the upper part of the jejunum might be one of the important factors in preventing the formation of jejunal ulcers after gastro-enterostomy. In 1914 Langenskiöld<sup>17</sup> performed the same operation which Mann later termed the "duodenal drainage operation." He severed the duodenum a short distance from the stomach and closed the distal end, sectioned the jejunum several centimeters below the junction of the duodenum with the jejunum, and joined the aboral end to the stump of the duodenum. The oral end of the jejunum he anastomosed to a loop of jejunum further caudad, thus shunting the duodenal, pancreatic and biliary secretions into the midportion of the small intestine. A month later an ulcer was found in the short segment of duodenum joining the stomach and jejunum. Prior to this, in 1898, Chlumsky<sup>18</sup> reported similar experiments in which he deviated all the duodenal secretions into the fundus of a gastro-enterostomized stomach, as was later done by McCann. Keppich,<sup>19</sup> in 1921, repeated Chlumsky's experiment, and in 2 dogs in which 6 cm. of the pars pylorica was left in connection with duodenum jejunal ulcers formed near the anastomosis. In 2 other animals the operation was modified to the extent that much of the distal end of the stomach was resected. In neither of these dogs did an ulcer occur. In 2 other animals he combined Chlumsky's and Langenskiöld's operations so as to deviate the duodenal juices into the fundus of a stomach which emptied through the pylorus into a short segment of duodenum and then into the jejunum; an ulcer did not form. From this work Keppich concluded that a mixture of pyloric and duodenal secretions is more likely to permit

---

14. Hughson, W.: Relation of Pylorus to Duration of Experimental Gastric Ulcer, *Arch. Surg.* **15**:66 (July) 1927.

15. Elman, R., and Rowlette, A. P.: The Rôle of the Pyloric Sphincter in the Behavior of Gastric Acidity, *Arch. Surg.* **22**:426 (March) 1931.

16. Bickel, A.: Beobachtungen an Hunden mit exstirpiertem Duodenum, *Berl. klin. Wchnschr.* **46**:1201, 1909.

17. Langenskiöld, F.: Ueber die Widerstandsfähigkeit einiger lebender Gewebe gegen die Einwirkung eiweisspaltender Enzyme, *Skandinav. Arch. f. Physiol.* **31**:1 1914.

18. Chlumsky, V.: Ueber die Gastroenterostomie, *Beitr. z. klin. Chir.* **20**:231 and 487, 1898.

19. Keppich, J.: Ueber das Ulcus pepticum Jejuni nach Pylorusausschaltung, *Zentralbl. f. Chir.* **48**:118, 1921; Künstliche Erzeugung von chronischen Magengeschwüren mittels Eingriffen am Magen-vagus, *Wien. klin. Wchnschr.* **34**:118, 1921.

the formation of a jejunal ulcer than the duodenal secretions alone. Koennecke,<sup>20</sup> in 1922, tested this theory by isolating the pars pylorica and the first portion of the duodenum (apparently above the openings of the pancreatic and biliary ducts), closing both ends and draining this segment into a loop of ileum. The main portion of the stomach was then drained into the second portion of the duodenum as in the Billroth operation I; ulcers did not form. When, in addition to this operation, he cut the splanchnic nerves on both sides, chronic duodenal ulcers developed in all 4 animals.

In 1910, Moutier<sup>21</sup> made a total gastric pouch, and in 3 of the animals a perforating gastric ulcer occurred. He made the further interesting observation that in these stomachs through which food did not pass the ulcers did not show the usual predilection for the lesser curvature. Similarly, Matthews and Dragstedt<sup>5</sup> obtained ulcers in a totally isolated stomach, as well as in a large Pavlov pouch accessory stomach, in both of which the motility of digestion was absent. They called attention to the fact that the remainder of the stomach from which the pouch was made did not ulcerate.

Kapsinow<sup>22</sup> was the first to deviate bile from the gastro-intestinal tract. He implanted the fundus of the gallbladder into the pelvis of the right kidney and subsequently ligated the common duct. His animals rapidly lost weight, passed tarry stools, and died after two or more weeks. At autopsy 17 of 40 animals had acquired single or multiple ulcers varying in size from 2.5 to 5 cm. in diameter with punched-out, overhanging edges. He stated that Whipple produced ulcers by making a biliary fistula and later ligating the common duct, but criticized the work because of the possibility that infection, ascending through the fistulous tract to the duodenum or the liver, and not biliary drainage, caused the ulcers. As Kapsinow's dogs were in poor condition before death, it is possible that inanition played some part in the production of the ulcers in his series. Mueller,<sup>23</sup> Köllicher,<sup>24</sup> Bidder,<sup>24</sup> Schmidt,<sup>21</sup> Beatti<sup>24</sup> and others produced ulcers "after exclusion of the liver." Boll-

20. Koennecke, W.: Experimentelle Untersuchungen über die Bedeutung des Pylorusmagens für die Ulcusgenese, *Arch. f. klin. Chir.* **120**:537, 1922; *Zentralbl. f. Chir.* **50**:276, 1923; *Ulcusgenese und Gastroenterostomie*, *ibid.* **53**:1866, 1926.

21. Moutier, F.: De l'ulcère chronique spontané chez le chien à estomac isolé, *Arch. d. mal. de l'app. digestif* **4**:49, 1910.

22. Kapsinow, R.: The Experimental Production of Duodenal Ulcer by Exclusion of Bile from the Intestine, *Ann. Surg.* **83**:614, 1926.

23. Mueller, Ludwig: Das corrosive Geschwür im Magen und Darmkanal (*Ulcus ventriculi perforans chronicum rotundum*), und dessen Behandlung, Stuttgart, Ferdinand Enke, 1860, p. 274.

24. Quoted by Greggio: Des ulcères gastro-duodénaux, *Arch. de méd. expér. et d'anat. path.* **27**:533, 1916-1917.

man and Mann<sup>25</sup> reported that perforating ulcers occurred when dogs were fed coarse food following partial hepatectomy, creation of a true Eck fistula and ligation of the common duct, procedures which probably influenced the quantity of bile entering the duodenum. In a second series of experiments they obtained similar results with usual diets after ligation of the common duct and removal of the gallbladder, and, in a few instances, after partial removal of the liver. Berg and Jobling,<sup>26</sup> by excluding bile, obtained ulcers in 4 of 7 dogs in which a biliary fistula was made, in 6 of 11 dogs in which a fistula was first made and then obstructed, and in 3 of 5 dogs in which the common duct was ligated. Ivy and Fauley<sup>27</sup> obtained duodenal ulcers in 2 of 20 dogs in which the common duct was obstructed; Morton also obtained ulcers after obstructing the common duct, and Ivy<sup>13</sup> noted ulcers in 6 of 10 dogs with permanent biliary fistulas.

Rous and McMaster,<sup>28</sup> using Berg and Jobling's<sup>26</sup> method of producing biliary drainage, were unable to obtain peptic ulcers. Elman,<sup>29</sup> using the same technic, observed no ulcers in many dogs, some of which were kept alive for as long as four months. Puestow,<sup>30</sup> in a study of biliary secretion following exteriorization of the duodenal segment containing the ampulla of Vater, made no mention of having observed ulcers. That ulcers did not develop in the animals of all of the latter investigators, who were able to keep their dogs in good condition for a period of months, suggests that some factor other than the absence of bile is responsible for the production of ulcers in the dogs with inanition. Since Ivy<sup>13</sup> has shown that ulcers are more likely to occur in experimental animals in poor condition, or with pneumonia, it seems probable that some of these dogs might have acquired ulcers because of their malnutrition and did not have malnutrition because of their ulcers. Certainly the dogs with obstruction of the biliary tract or with removal of part or all of it (hepatectomy) had sufficient metabolic

---

25. Bollman, J. L., and Mann, F. C.: Chronic Duodenal Ulcer in Animals with Eck Fistulas on Certain Diets, *Arch. Path.* **4**:492 (Sept.) 1927; Peptic Ulcer in Experimental Obstructive Jaundice, *Arch. Surg.* **24**:126 (Jan.) 1932.

26. Berg, B. N., and Jobling, J. W.: Biliary and Hepatic Factors in Peptic Ulcers, *Arch. Surg.* **20**:997 (June) 1930.

27. Ivy, A. C., and Fauley, G. B.: Chronicity of Ulcer in the Stomach and Upper Intestine, *Am. J. Surg.* **11**:531, 1931.

28. Rous, P., and McMaster, P. D.: Method for the Permanent Sterile Drainage of Intra-Abdominal Ducts as Applied to the Common Duct, *J. Exper. Med.* **37**:11, 1923.

29. Elman, R.: Gastric Acidity in Pancreatic Drainage, *Arch. Surg.* **16**:1256 (June) 1928; Spontaneous Peptic Ulcers of the Duodenum Following the Total Loss of Pancreatic Juice, *ibid.* **23**:1030 (Dec.) 1931.

30. Puestow, C. B.: The Activity of Isolated Intestinal Segments, *Arch. Surg.* **24**:565 (April) 1932.

disturbances to acquire ulcers as a result of more than one factor. An experiment herein reported definitely indicates that the deviation of bile alone from the duodenum does not result in the formation of peptic ulcer.

Deviation of pancreatic secretion alone into the lower intestinal tract has not been reported. However, by exclusion or total loss of the pancreatic juice, Elman and Hartmann<sup>31</sup> obtained duodenal ulcers in 6 dogs in which they accomplished pancreatic drainage. They were able to keep their animals alive for at least thirteen days by means of intraperitoneal injections of lactate Ringer's solution (as devised by Dr. Hartmann) in 5 per cent dextrose. Jona,<sup>32</sup> after tying the pancreatic duct in 11 animals, found ulcers in the duodenum, the stomach and the jejunum, and Gallagher<sup>33</sup> observed delayed healing of traumatic ulcers after ligation of the duct. In view of the alkalinity and large quantity of the pancreatic secretion it seems reasonable that the absence of its neutralizing effect might have delayed healing in the latter's animals, but experiments herein included do not substantiate the work of Elman and Hartmann.<sup>31</sup> It seems that the ulcers obtained by Jona<sup>32</sup> could have been due to other factors than the absence of the neutralizing effect of pancreatic juice.

The combined elimination of bile and pancreatic juice was first done by Kehrer.<sup>34</sup> He implanted the pancreatic duct in the appendix and anastomosed the gallbladder to the same viscus after ligating the common duct. In 6 dogs that died he found lesions which were macroscopically and microscopically typical peptic ulcers. Grey<sup>35</sup> likewise obtained ulcers in 2 dogs after transplanting the bile and pancreatic ducts into the terminal ileum. Mann and Williamson<sup>36</sup> transplanted both the bile and the pancreatic ducts into the lower part of the ileum and obtained single and multiple indurated ulcers in the region between

---

31. Elman, R., and Hartmann, A. F.: Spontaneous Peptic Ulcers of the Duodenum After Continued Loss of Total Pancreatic Juice, *Arch. Surg.* **23**:1030 (Dec.) 1931.

32. Jona, J. L.: A Further Contribution to the Experimental Study of Duodenal Ulcer, *M. J. Australia* **1**:316, 1919; Experimental Study of Duodenal Uleer, *Physiol. Abstr.* **4**:412, 1919.

33. Gallagher, W. J.: Acute Traumatic Ulcers of the Small Intestine: Observations on the Effects of the Application of Clamps on the Gastro-Intestinal Tract; an Experimental Study, *Arch. Surg.* **15**:689 (Nov.) 1927; Acid on Jejunal Transplants, *ibid.* **17**:279 (Aug.) 1928; Acid on Peptic Uleer, *ibid.* **17**:613 (Oct.) 1928.

34. Kehrer, J. K. W.: Ueber die Ursache des runden Magengeschwürs, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **27**:679, 1914.

35. Grey, E. G.: Duodenectomy: Its Effect upon the Life of an Animal, *Surg., Gynec. & Obst.* **28**:36, 1919.

36. Mann, F. C., and Williamson, C. S.: The Experimental Production of Peptic Ulcer, *Ann. Surg.* **77**:409, 1922.

the pylorus and the ampulla of Vater in 10 of 31 dogs. Ulcers occurred in 8 of 10 dogs in which they removed the entire duodenum, anastomosed the proximal end of the jejunum to the pylorus, and transplanted the bile and pancreatic ducts into the terminal ileum.

Mann and Williamson<sup>36</sup> reinitiated the study of ulcer formation following the deviation of all the alkaline duodenal contents into the lower intestinal tract. In 14 of 16 dogs subjected to "duodenal drainage," subacute or chronic ulcers similar to those found in man occurred in the third or fourth week on the posterolateral surface of the jejunum, just distal to the jejuno-pyloric anastomosis, whereas ulcers developed in only 2 of 10 dogs in which they resected the duodenum and transplanted the bile and pancreatic ducts into the jejunum near the point where the latter was anastomosed to the pylorus. According to McCann,<sup>2</sup> "In duodenal drainage Mann conceived of the gastric chyme as being ejected through the pylorus by gastric contractions, as if through a nozzle and impinging forcibly against the wall of a segment containing little, if any, alkali, the mechanical and chemical action of this stream leading to necrosis of the epithelium and the formation of ulcer."

By several experimental methods Morton<sup>2</sup> further confirmed the probability that the chronicity of ulcers and their failure to heal were due to the action of unneutralized acid gastric chyme and trauma. He excised pieces of mucosa from the lesser and greater curvatures of the stomach in 36 dogs and instituted "duodenal drainage." In from 50 to 62 per cent of these the defects in the antrum and on the lesser curvature were still present at subsequent observations. Similar defects in control animals healed within two weeks. Morton<sup>2</sup> believed that the defects on the lesser curvature persisted longer because they were subject to more trauma than those on the greater curvature. In 13 animals he transplanted jejunal "patches" with intact circulation into the gastric wall, and in addition performed "duodenal drainage." In 4 of these dogs ulcers developed in the "patches" on the lesser curvature, whereas no ulcers occurred on the greater curvature. Jejunal transplants in control dogs showed no marginal ulceration after fifteen days.

In the duodenum Mann and Williamson<sup>36</sup> believed that the mechanical factor contributing to the cause of ulcer was the force of the impinging stream of gastric chyme through the pylorus. In the stomach Morton<sup>2</sup> believed that the mechanical factors which localized the ulcers obtained by him were "the paucity of protecting rugae in the prepyloric segment, particularly along the 'Magenstrasse' with its poor blood supply and the convergence of the lines of force along the lesser curvature as suggested by Aschoff."

McCann<sup>3</sup> modified the original "duodenal drainage" operation to shunt the alkaline duodenal secretions from the distal side of the pylorus to the gastric side. His assumption was that the deviation of duodenal

contents into the fundus of the stomach might control gastric acidity. A test meal of meat and water given to 2 dogs preoperatively and postoperatively revealed, by fractional analysis, the same normal curves for free hydrochloric acid, total acid and combined chlorides before and after "modified duodenal drainage." Fractional gastric analyses before and after the performance of the original "duodenal drainage" operation revealed similar curves. On the basis of these findings, McCann<sup>3</sup> concluded that the mechanism for control of gastric acidity is intragastric, and that the level of gastric acidity is wholly independent of reflux of duodenal contents. This phase of McCann's work is open to criticism because only 2 animals were used, and the meat test meal which was given usually combines readily with hydrochloric acid to mask the actual acidity developed. Contradictory findings have been reported by Steinberg, Brougher and Vidgoff,<sup>37</sup> who, by the use of a test meal of 300 cc. of water containing extract of beef, observed a much higher acidity following "duodenal drainage" into the terminal ileum than was obtained in the normal stomach. These workers contended that the difference in acidity was not due to hypersecretion on the part of the stomach, since the acidity of a Pavlov pouch in the same animal remained unaltered.

McCann<sup>3</sup> obtained single or multiple subacute and chronic ulcers in the upper jejunum in 21 of 26 dogs on which he had performed his "modified duodenal drainage operation." The incidence and type of ulcers were the same as those obtained by Mann, but he emphasized trauma as a factor in the production of these ulcers more than the action of unneutralized acid gastric chyme. In one specimen hairs were embedded in the wall of the ulcer, and in another an ulcer that had perforated was plugged by a pyramidal piece of turnip. These, he believed, were implanted in the ulcer by the forceful impinging of the gastric contents onto the jejunum and the friction of coarse cellulose foods. He was particularly impressed with the forceful ejection of gastric chyme, because he observed roentgenologically that the whole prepyloric segment was thrown into a vigorous tonic contraction when a test meal was given.

Because the ulcers in his experiments developed in the presence of an unneutralized normal gastric acidity, McCann concluded that the alkaline duodenal contents protect against ulcer formation "by some type of buffer or diluting action beyond the pylorus that terminates the acid peptic activity of the gastric chyme." That the gastric acidity might have been abnormally high, particularly when the original "duo-

---

37. Steinberg, M. E.; Brougher, J. C., and Vidgoff, I. J.: Changes in the Chemistry of the Contents of the Stomach Following Gastric Operations, *Arch. Surg.* 15:749 (Nov.) 1927.

denal drainage" was performed, has been commented on. That it was abnormally high after the modified operation is not improbable, for it is possible that gastric peristalsis forced gastric contents retrogradely into the duodenal loop or at least seriously interfered at times with the free and continuous flow of the duodenal contents into the stomach.

Steinberg and Proffitt<sup>38</sup> also believed that trauma plays a part in the production of the ulcers that occur in animals subjected to "surgical duodenal drainage." They found that ulcers occurred just distal to the anastomosis in 100 per cent of dogs when the jejunum was anastomosed end-to-end with the pylorus, whereas if the side of the jejunum was anastomosed to the end of a pylorctomized stomach, ulcers were obtained in only 43 per cent of the animals. They also observed that following the latter Billroth type of anastomosis ulcers occurred more frequently when they produced a kink just distal to the anastomosis. This, they believed, produced stasis and allowed the acid gastric chyme more time to exert its corrosive action.

The experiments of Matthews and Dragstedt<sup>5</sup> indicate that the action of acid gastric juice is more important than trauma in the production of peptic ulcer. They reproduced in dogs a counterpart of the Meckel's diverticulum of man by implanting a small isolated pouch of gastric wall into the jejunum and into the ileum. In the intestinal mucosa near the transplant, chronic ulcers occurred in 85 per cent of instances in the jejunum and in 100 per cent in the ileum. These ulcers occurred in the absence of unaccustomed trauma and could have been produced only by the corrosive action of acid gastric juice. These authors repeated the "duodenal drainage" experiment, but anastomosed the duodenum to the jejunum only 40 cm. below the anastomosis of the jejunum with the pylorus. Only 1 dog of 21 so operated on acquired a jejunal ulcer. In this experiment regurgitation of duodenal contents apparently prevented the formation of ulcers, and the trauma emphasized by McCann<sup>3</sup> was evidently not great enough to produce destruction of the jejunum. In another group of animals in which the pyloric musculature was completely excised and regurgitation prevented by placing a one-way valve above the point of drainage of the duodenal contents into the jejunum, ulcers developed in 100 per cent, showing that the corrosive action of unneutralized acid gastric juice alone will cause ulcer formation. When in normal dogs a valve was placed in the pylorus to prevent regurgitation of duodenal contents, both the free and the total acidity in the gastric contents were raised above normal when a standard test meal was given. Neutralization of 0.5 per cent hydrochloric acid placed in the stomach was delayed, as was the healing of

38. Steinberg, M. E., and Proffitt, J. C.: The Etiology of Postoperative Peptic Ulcers, *Arch. Surg.* 25:819 (Nov.) 1932.



acute ulcers produced by the injection of silver nitrate into the gastric mucosa. Prevention of regurgitation of duodenal contents also resulted in the occurrence of ulcers in transplants of intestinal mucosa sutured into defects made in the gastric mucosa. Matthews and Dragstedt<sup>5</sup> believed that these experiments substantially support the contention that the chemical action of pepsin hydrochloric acid (of the concentration found in pure gastric juice) can by itself produce typical chronic peptic ulcer. They stated that it should be emphasized that no evidence has been offered which contradicts the possible deterrent action of gastric motility and the mechanical action of coarse food in the healing of acute lesions of the stomach or duodenum. They concluded, however, that of these three factors, the chemical action of the acid gastric secretion seems to be the most important both in the production of acute peptic ulcer and in its subsequent chronicity.

The following investigations were undertaken in order to evaluate the effect of trauma in the production of peptic ulcers and to determine the combined and relative values of bile and pancreatic juice in the prevention of ulcer.

#### I. EFFECTS PRODUCED BY DRAINAGE OF THE DUODENAL CONTENTS INTO THE PREPYLORIC SEGMENT OF THE STOMACH

This study on the etiology of peptic ulcer is based on the well known experimental evidence that ulcers develop just distal to the anastomosis of the jejunum and the pylorus in 100 per cent of dogs when "surgical duodenal drainage" is performed. To evaluate better the rôles played by trauma and unneutralized acid gastric contents, a modified duodenal drainage operation (fig. 1) was performed in order that duodenal reflux could be mimicked. The duodenal contents instead of being deviated into the fundus of the stomach, as was done by McCann,<sup>3</sup> were deviated into the prepyloric portion of the stomach just proximal to the anastomosis of the pylorus with the jejunum (fig. 1). By this means the alkaline secretions could mix with the acid gastric contents as they were ejected from the stomach and possibly neutralize these to such an extent that ulceration in the jejunum would not occur unless trauma, as is emphasized by McCann,<sup>3</sup> is an important factor in the production of ulcer.

#### METHOD

Moderately large healthy dogs that were already accustomed to kennel life were used in these experiments. The surgical procedure was performed under aseptic conditions. Rubber-covered spring steel clamps were used to facilitate the making of the anastomoses, but no crushing clamps were used on tissue that was to be included in the anastomotic sutures. Silk was used throughout as suture material.

The abdomen was opened by a high midline incision. The pylorus was delivered into the wound, and the vessels on the upper and lower borders were clamped, divided and tied with silk. The pylorus was divided, and the duodenal end was ligated, inverted by a purse-string suture and covered with a piece of the hepaticoduodenal ligament. Just distal to the ligament of Treitz the jejunum was delivered and divided. The proximal end of the distal segment was anastomosed to the pyloric end of the stomach to reestablish continuity of the gastro-intestinal tract with the duodenum excluded. The distal or jejunal end of the isolated duodenum was anastomosed (end-to-side) to the prepyloric portion of the anterior wall of the stomach within 3 cm. of the jejunopyloric anastomosis (fig. 1).

By means of this technic the alkaline duodenal contents were shifted from the distal side of the pylorus to the proximal side at a point very near the pyloro-jejunal anastomosis so that gastric contents might be mixed with duodenal contents just as the former passed out of the stomach. It was thought that the mixing of acid gastric chyme and alkaline duodenal contents obtained in this manner would

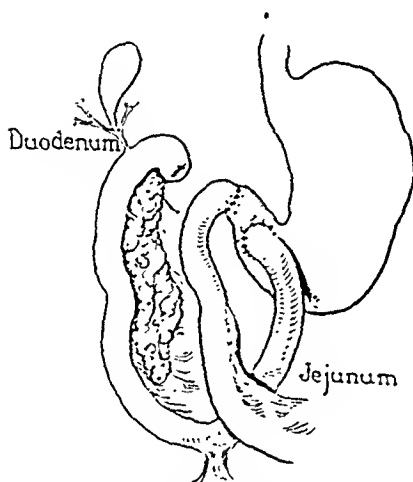


Fig. 1.—Drawing illustrating the "duodenal drainage operation" modified to mimic duodenal reflux by deviation of duodenal contents into the prepyloric portion of the stomach.

simulate to some extent that which is supposed to occur if reflux of duodenal contents actually does take place. The question was: Would the susceptible jejunal mucosa ulcerate in the presence of controlled gastric acidity, but under conditions permitting as much traumatization as occurs in the operations of Mann<sup>1</sup> and McCann?<sup>2</sup>

After operation the dogs were fed milk and syrup until they were able to take ordinary kennel rations, which consisted of coarsely ground up bones and foods of all sorts.

#### RESULTS

Eleven dogs lived from thirty to one hundred and eighteen days. In several of the dogs that died earlier no definite cause of death could be found, but these animals appeared to have an intoxication similar to that seen in animals with a high intestinal obstruction. As the prepyloric muscle is very thick and was usually found contracted at

necropsy, it seems not unlikely that this musculature exerted on the gastrojejunostomy a sphincteric action which caused a partial or intermittent obstruction of the duodenal segment. The 11 dogs that survived longer periods progressively lost weight and strength and died of inanition. In most instances the duodenal segment was sufficiently dilated and bile-stained to suggest that there had been a stasis of duodenal contents. In none of the dogs did a subacute or chronic ulcer develop in either the stomach or the jejunum.

#### COMMENT

The fact that peptic ulcers did not develop when the duodenal contents were deviated into the prepyloric portion of the stomach instead of into the fundic portion, as was done by McCann,<sup>3</sup> seems to indicate that the acid gastric chyme as it passed, or was ejected from, the pyloric end of the stomach into the jejunum, was sufficiently mixed with alkaline duodenal secretions to render it noninjurious to jejunal mucosa. That normal physiologic reflux of duodenal contents was duplicated is not claimed, for it is doubtful that the jejunum was bathed by alkaline duodenal contents more than a part of the time, but it is probable that the oncoming acid gastric contents were neutralized or diluted much in the same manner as they are by the reflux of alkaline duodenal contents. It is evident from these results that trauma is of little importance as a factor in the production of ulcer by "duodenal drainage."

That trauma plays an important rôle in the production of peptic ulcers following "surgical duodenal drainage," as believed by Mann,<sup>36</sup> McCann<sup>3</sup> and their associates, is not substantiated, as in this experiment "the force of the impinging stream ejected through the pylorus" was not altered, and ulcers did not form.

#### II. STUDY OF BILE AND PANCREATIC JUICE, RESPECTIVELY, IN THE PREVENTION OF EXPERIMENTAL PEPTIC ULCER

This study was undertaken to evaluate the rôles played by bile and pancreatic juice, respectively, in the prevention of peptic ulcer. By previous investigators these alkaline secretions had been simultaneously deviated, and each had been separately excluded by drainage to the outside, but each had not been separately deviated into the lower intestinal tract. Various authors, without basing conclusions on experimental evidence, had claimed greater neutralizing properties for one than for the other. These properties, the degree of alkalinity and the quantity of each secretion, had been accurately estimated, but their physiologic action *in situ* had not previously been determined.

In the present investigation, deviation of bile was obtained by ligating and dividing the common duct and anastomosing the fundus of the

gallbladder to the terminal portion of the jejunum (fig. 2). Deviation of the pancreatic juice was accomplished by transplantation of the main pancreatic duct into the terminal portion of the jejunum and ligation or avulsion of the accessory pancreatic duct (fig. 3).

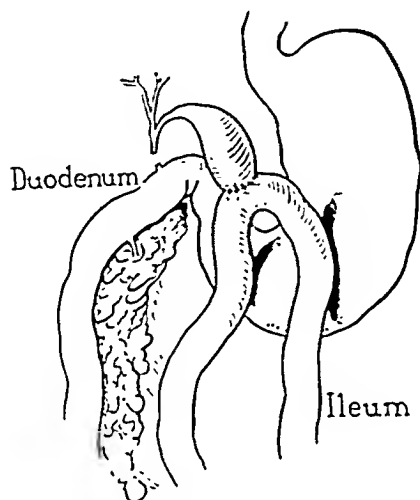


Fig. 2.—Drawing illustrating the deviation of bile into the terminal portion of the jejunum by an operation in which the common duct was divided and the gallbladder anastomosed to the jejunum.

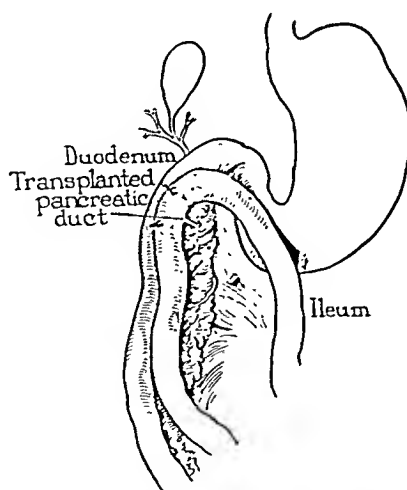


Fig. 3.—Drawing illustrating the deviation of pancreatic juice into the terminal portion of the jejunum by transplantation of the main pancreatic duct into the jejunum.

#### METHODS

Moderately small dogs were used in this study because in large animals the deep thorax was found to make the operative procedures extremely difficult.

*Deviation of Bile* (fig. 2).—The common bile duct was identified and sectioned between two ligatures placed just adjacent to the entrance of the duct into the

duodenum. The fundus of the gallbladder was delivered into the operative field with the aid of Allis clamps, which, after aspiration of the contents of the gallbladder, were replaced by "guy sutures" to facilitate making the anastomosis with the terminal portion of the jejunum. The stoma made in the two organs was usually less than 5 mm. in length. Some anastomoses were executed with a single row of silk mattress sutures, but in most of them a continuous silk Lembert suture was used in addition to a through and through continuous catgut hemostatic suture. In 3 of the dogs jejunojejunostomy was performed adjacent to the described anastomosis to short circuit intestinal contents away from the cholecystojejunostomy.

*Deviation of Pancreatic Juice* (fig. 3).—The small accessory pancreatic duct, which enters the duodenum 0.5 cm. below the papilla of Vater, was identified and either avulsed or ligated. The main pancreatic duct (about 3 mm. in diameter), which enters the duodenum about 4 cm. below the papilla of Vater, was identified and "reamed" out of the duodenum so that approximately 2 mm. of duodenal wall remained about its os. The resulting defect in the duodenum was closed with a single row of interrupted Lembert sutures, which did not invert enough tissue to produce a duodenal atresia. The distal portion of the jejunum was identified, and two silk sutures were passed through its medial wall into the lumen and out through a small stab wound placed in the opposite side of the gut. These sutures were then passed through the muscle and submucosa surrounding the os of the pancreatic duct and were brought back through the stab wound to cross the lumen and come out through the jejunal wall near their starting points. By means of these sutures the stump of the pancreatic duct was carefully introduced and drawn through the stab wound into the lumen of the jejunum and was then made fast by tying these sutures. A few Lembert sutures were employed to approximate the jejunum and duodenum, thus avoiding undue tension on the sutures holding the pancreatic duct in the lumen of the jejunum.

## RESULTS

Fourteen dogs were subjected to deviation of bile (fig. 2) by division of the common duct and anastomosis of the fundus of the gallbladder with the end-portion of the jejunum. Six dogs died in two weeks or less of shock or peritonitis. Eight dogs lived long enough to make them of experimental value; 1 is still alive and healthy after eleven months, 4 lived three months or longer, and 3 died one month after operation. Death was due in most instances to hepatitis or to pneumonia produced by migration of *Dirofilariae* from the heart into the lesser circulatory system whence they perforated to cause a hemorrhagic pneumonitis. In only 1 of the 8 dogs was an ulcer observed at autopsy. This ulcer occurred just distal to the pylorus and caused death of the animal in three months by a spontaneous healing which produced a duodenal stenosis. In all of the other animals the duodenal and gastric mucosa were apparently normal.

Eight dogs were subjected to deviation of the pancreatic juice (fig. 3) by transplantation of the pancreatic duct into the terminal portion of the jejunum. Three of the 8 dogs did not live long enough to be of experimental value, but the remaining 5 lived from two to four months.

Death was due to pneumonia produced by *Dirofilariae*. In none of the dogs was an ulcer observed, and in all instances the duodenal and gastric mucosa appeared grossly normal.

#### COMMENT

As Mann<sup>36</sup> had obtained experimental peptic ulcers of the duodenum in 20 per cent of dogs in which he had deviated the alkaline bile and pancreatic juice simultaneously to the lower intestinal tract, it was hoped that ulcers could be produced in the absence of one of the alkaline digestive juices (figs. 2 and 3). Had a fairly high incidence of duodenal ulcer occurred in the absence of either one of these alkaline digestive juices, some valuable information would have been obtained concerning the comparative protective value of either of them. The finding of a completely healed ulcer in the duodenum of 1 animal that was subjected to deviation of the bile does not justify drawing any conclusions concerning the comparative protective value of bile and pancreatic juice in preventing ulcer. The ulcer was merely an acute one which in the presence of pancreatic juice healed spontaneously. On the basis of the negative results obtained in this experiment one is probably justified in concluding that either bile or pancreatic juice alone does protect against ulcer formation. That the duodenal mucosa is highly resistant to ulcer formation is self-evident, especially when one considers that prompt healing occurred in the sutured defect caused by the "reaming" out of the pancreatic duct.

#### III. EFFECT OF ACID GASTRIC CHYME ON DUODENAL AND JEJUNAL MUCOSAE WHEN NEUTRALIZED BY BILE OR PANCREATIC JUICE ALONE

In this study experiments were carried out to determine the effect that bile or pancreatic juice, respectively, might have in the prevention of ulcer in duodenal and jejunal mucosae exposed to acid gastric chyme. Similar investigations had not previously been made. Bile and pancreatic juice, respectively, had been excluded by drainage to the outside or by ligating the common or pancreatic ducts, but their protective effects in either the duodenum or the jejunum had not been comparatively studied.

On the deviation of bile into the lower intestinal tract, pancreatic juice alone remained in the duodenum to counteract the corrosive action of acid gastric contents. Conversely, when pancreatic juice was deviated, bile remained alone to protect the duodenum.

When the foregoing deviations had been present long enough to be of experimental value, duodenal drainage was instituted. The jejunal loops which had formerly received bile (fig. 1) or pancreatic duct (fig. 4) transplantations were anastomosed to the antral end of the

stomach in order to determine the comparative protective values that either of the alkaline digestive juices might have in a jejunum exposed to the action of acid gastric chyme.

#### METHODS

Moderately large, well nourished dogs that had already become accustomed to kennel life were utilized, to lessen the risk of losing the animals before observations might be completed.

*Deviation of Bile.*—The common bile duct was identified and sectioned between mosquito forceps and a ligature placed just proximal to where the duct enters the duodenum. After the duct had been dissected free for 2 cm., two mosquito forceps were placed on the end of it, and between these the duct was split about 2 mm. upward. At a point on the jejunum about 30 cm. beyond the ligament of

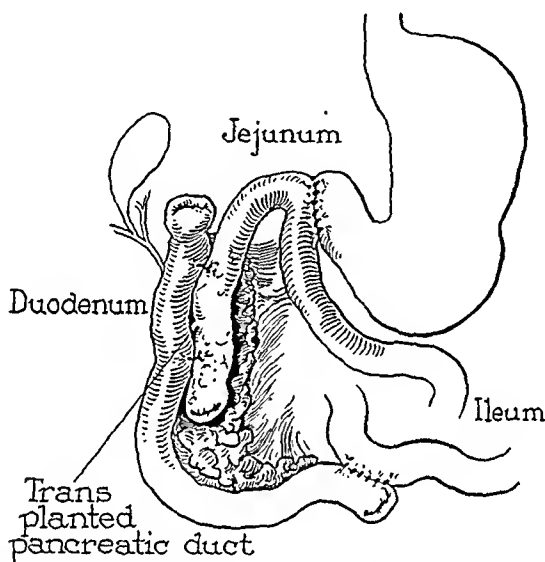


Fig. 4.—Drawing illustrating the duodenum containing bile drained into the ileum and substitution for it of the jejunum containing the transplanted pancreatic duct.

Treitz sutures were placed as in study II, and the duct was drawn through a stab wound into the lumen of the jejunum and secured. A few Lambert sutures were placed to approximate the jejunum and duodenum to lessen undue tension of the transplant. The loop of jejunum utilized was placed so that it ran upward and parallel to the duodenum in order that it might satisfactorily serve for the second part of this study.

*Deviation of Pancreatic Juice.*—This was accomplished as in study II, except that the transplant was made in the jejunum at a point 30 cm. beyond the ligament of Treitz.

*Substitution of Jejunum Containing Transplant for Duodenum* (figs. 4 and 5).—After the animals subjected to the two preceding transplantations had served their purpose they were reoperated on. The stomach was sectioned proximal to the pylorus and the end of the duodenum with the attached pars pylorica was closed with through and through and Lembert sutures. Next the jejunum was sectioned

a few centimeters below the duct transplant. The end leading up to the transplant was closed, and the proximal or duodenal end was anastomosed into the distal portion of the ileum. The loop of jejunum containing the transplant was placed so that it led up into the upper right quadrant of the abdomen and then turned downward so that its antimesenteric border could be anastomosed, end-to-side, with the stomach. The latter anastomosis was accomplished with continuous silk sutures for both the mucosa and the serosa (figs. 4 and 5).

Immediately following operation the dogs received an infusion and were subsequently fed in the same manner until the sixth day. They were then given dextrose and milk until the ninth day, when they were placed on regular kennel rations.

### RESULTS

After transplantation of either the common or the pancreatic duct the dogs were allowed to go from twenty-three to fifty-two days (aver-

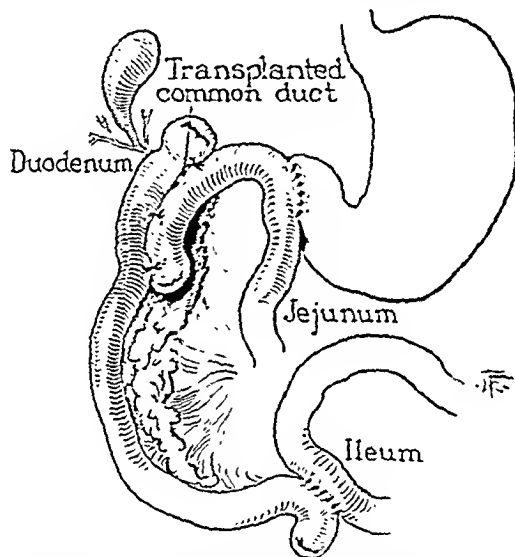


Fig. 5.—Drawing illustrating the duodenum containing pancreatic juice drained into the ileum and substitution for it of the jejunum containing the transplanted common duct.

age of thirty-five days) before they were subjected to the second operation. Twelve dogs were subjected to reoperation, and in neither group of 6 each was a duodenal ulcer found on exploration. Likewise there were no ulcers in 2 additional dogs, 1 from each group, that died four weeks and one week after the original operation. In these 14 dogs the failure of ulcers to form in the duodenum substantiates the results obtained in study II and increases the number of dogs subjected to deviation of bile to 15 and to deviation of pancreatic juice to 12.

Of the 7 dogs on which transplantation of the common duct had been performed, 6 were reoperated on from twenty-one to fifty-one days later (average of thirty days). After "surgical duodenal drainage" (fig. 5) or excluding the duodenum and substituting the jejunum



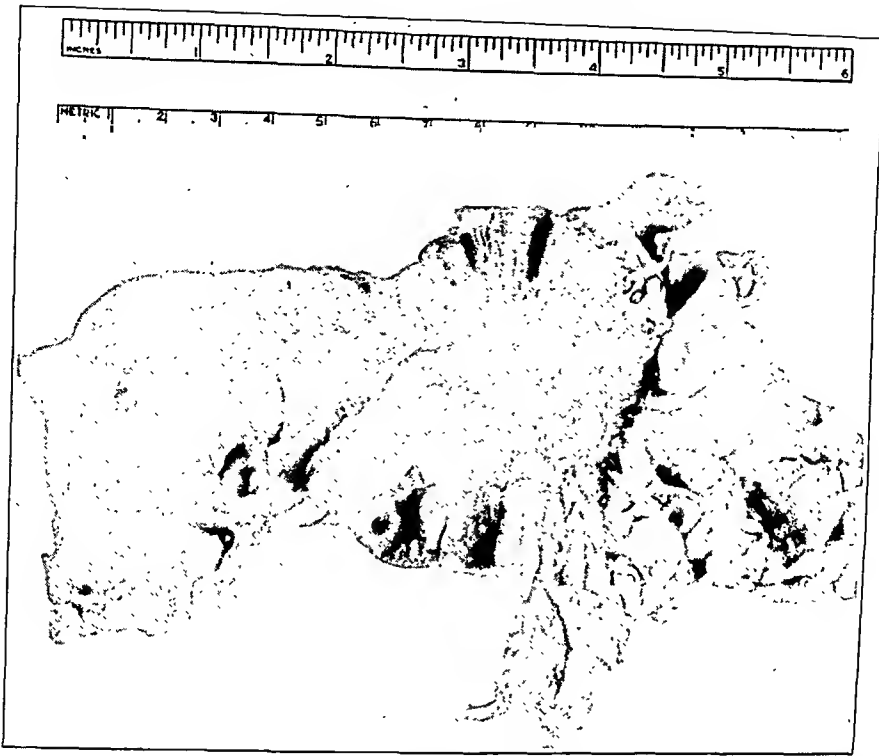


Fig. 6.—Photograph showing a huge callous ulcer and two smaller chronic ones obtained in a jejunum protected by bile alone.

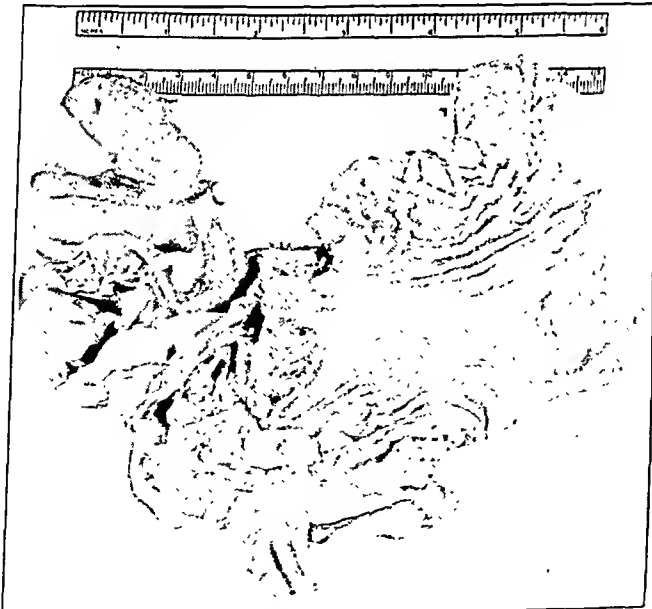


Fig. 7.—Photograph showing an ulcer that had perforated and four smaller ones obtained in a jejunum protected by bile alone.

with its common duct transplant, 1 dog died of pneumonia on the tenth day. No ulcer was present, but erosion was evident about the silk sutures. The five remaining dogs all died in from twenty-two to fifty days with ulcers of the jejunum that had either perforated or caused a fatal hemorrhage. Most of the ulcers occurred within 2 cm. of the gastrojejunostomy, and all were of the chronic type seen in man. In an animal that bled to death a callous ulcer measuring 4 by 5 cm. had caused adhesions to a neighboring loop of intestine. Distal to this huge



Fig. 8.—Photograph showing a perforating ulcer obtained in a jejunum protected by bile alone.

ulcer were two smaller chronic ones (fig. 6). In another animal in which the ulcer perforated there were four smaller chronic ones further down in the jejunum (fig. 7). In the other 3 animals, in addition to a large perforating ulcer, there were also one or two small chronic lesions.

Of 7 dogs on which transplantation of the pancreatic duct had been performed, 6 were reoperated on. After the duodenum had been excluded and the jejunum with its pancreatic duct transplant (fig. 4) substituted, 1 dog died with pneumonia on the eighth day without an

ulcer. The 5 remaining dogs all died in from fourteen to forty days with ulcers, three of which perforated (fig. 8) and two of which caused a fatal hemorrhage (fig. 9). All of the ulcers were of the chronic type and occurred within 1 cm. of the gastrojejunosomy, being multiple in only 1 dog. In this animal there were two additional small callous ulcers.



Fig. 9.—Photograph showing a superficial ulcer obtained in jejunal mucosa protected by pancreatic juice alone.

#### COMMENT

In 14 dogs, common duct and pancreatic duct transplantations which deprived the normal duodenum of one or the other of the alkaline digestive juices were not followed by the occurrence of peptic ulcers, as was also shown in study II. In the former study bile was deviated by anastomosing the fundus of the gallbladder into the ileum, because this seemed technically easier than transplanting the common duct itself. However, the converse has proved easier, and it is not attended by hepatitis from retrograde filling of the gallbladder by intestinal contents.

Following transplantation of the common duct, for example, the pancreatic juice remained to protect the duodenal mucosa, but following the second operation ("duodenal drainage"; fig. 5) there was only bile to protect the jejunum substituted for the duodenum. In the other group of dogs the converse was true (fig. 4). The fact that peptic ulcers caused fatalities in all of the 5 dogs in each group that lived long enough for experimental purposes proves that the jejunal mucosa is more sensitive to the formation of peptic ulcer than is the duodenal mucosa. It was hoped that pancreatic juice could be definitely shown to be more protective than bile, but the results merely suggest this. The ulcers that occurred in the jejunum protected by pancreatic juice were actually not so large (fig. 8), not so prone to perforate (fig. 9) (three perforated) and not so often multiple (1 dog with multiple ulcer) as were those that occurred when bile was deviated to protect (four ulcers perforated, and in all dogs there were multiple ulcers; figs. 6 and 7). That neither of the alkaline digestive juices can prevent the formation of ulcers in jejunal mucosa exposed to the corrosive action of acid gastric chyme is definitely demonstrated in these experiments.

#### SUMMARY AND CONCLUSIONS

When "duodenal drainage" was performed and alkaline duodenal contents were deviated into the stomach just proximal to the pyloro-jejunal anastomosis (experiment I) ulcers did not form. This indicates that the neutralization of acid gastric chyme as it passed through the pylorus prevented the formation of ulcers. It does not substantiate the belief of McCann<sup>3</sup> that trauma is of great importance in the production of ulcers following "duodenal drainage."

If either bile or pancreatic juice was deviated from the duodenum into the lower intestinal tract (experiments II and III) the remaining duodenal contents were sufficient in quantity and alkalinity to prevent ulceration of the duodenum.

After the performance of "duodenal drainage" and transplantation of either the common bile duct or the pancreatic duct into the jejunum near the pylorojejunal anastomosis (experiment III) chronic or perforating peptic ulcers formed in all instances. The characters of the ulcers suggested that pancreatic juice may be more protective than bile.

# CHRONIC ULCERATIVE COLITIS WITH ASSO- CIATED CARCINOMA

## PROGRESS IN MANAGEMENT

J. ARNOLD BARGEN, M.D.

AND

CLAUDE F. DIXON, M.D.

ROCHESTER, MINN.

In 1928, one of us (Dr. Bargaen)<sup>1</sup> reported nineteen cases encountered at the Mayo Clinic in which a malignant neoplasm was associated with a lesion of long-standing, chronic ulcerative colitis and one case of lymphatic leukemia associated with progressive, fulminating, chronic ulcerative colitis. In three of the nineteen cases proof of a malignant condition lay in the development of a large filling defect in the colon, with a sudden and rapid change of symptoms and with signs of obstruction, cachexia and anemia; in fourteen cases a specimen removed either at operation or at necropsy established the diagnosis of carcinoma, and in two cases, the diagnosis of lymphosarcoma.

The cases in this series had many striking features in common. The sudden change in symptoms, the rapid failure of the patients, the apparent futility of treatment and the early demise of the patients were noteworthy. Of the twenty patients only one who underwent resection of the diseased portion of the colon for carcinoma and only one who underwent resection of a large section of the bowel for lymphosarcoma are living today. All of the rest died within from several days to several months after discovery of the malignant process. Most of them died within several weeks, irrespective of the treatment employed.

Polypoid hyperplasia of the inflamed mucous membrane was noted when the patients came under observation prior to the development of actual malignant disease. In more than a third of the cases polyps were found in the rectum at the time of proctoscopic examination before carcinoma appeared. We made a detailed report<sup>2</sup> of this association of polyps and chronic ulcerative colitis in 1930 and found polyps in 10 per cent of all of the cases of long-standing chronic ulcerative colitis. If polyps occur subsequently, therefore, in 10 per cent of cases of chronic ulcerative colitis and if in more than 60 per cent of the cases

---

From the Division of Medicine and the Division of Surgery, the Mayo Clinic.

1. Bargaen, J. A.: *Chronic Ulcerative Colitis Associated with Malignant Disease*, *Arch. Surg.* **17**:561 (Oct.) 1928.

2. Bargaen, J. A., and Comfort, M. W.: *The Association of Chronic Ulcerative Colitis and Multiple Polyps*, *Ann. Int. Med.* **4**:122 (Aug.) 1930.

in which carcinoma develops later the patient has passed through the stage of polyposis, it seems that the presence of polyps and the destructive infection of this type of colitis may predispose to carcinoma. Proof of this is lacking, but a study<sup>3</sup> in 1933 strongly suggested the presence of a neoplastic factor in chronic ulcerative colitis. Because of this, a further review of the cases reported in 1928 and some observed since then was undertaken to see if the newer clinical data might add information of value from the therapeutic standpoint.

The present study concerns twenty-five cases of carcinoma and two of lymphosarcoma proved at pathologic examination, the tumor developing in the course of severe chronic ulcerative colitis. The cases of the former report are included here, but they are considered principally from the standpoint of management. Of the twenty-seven patients, twelve were women and fifteen were men. The ages of the patients at the time of discovery of the carcinoma ranged from 21 to 69 years. In the cases of the younger patients the history of colitis was particularly likely to be long, and many of them had presented clinical and pathologic evidence of colitis for years.

A sudden change of symptoms with unusual bleeding and local pain in patients who had been under repeated observation was considered to be indicative of the onset of carcinoma. No one knows how long it takes a subclinical carcinoma to assume symptomatic proportions, but judging from the fulminating course of the disease after the change in symptoms and from the actual observation of pathologic change, the history of carcinoma is probably fairly accurately represented by the time given in table 1.

In case 1, the diagnosis of ulcerative colitis was established by proctoscopic examination as early as 1915, when the patient was 9 years of age. Since little encouragement could be given, the patient was not seen at the clinic again until 1924. In these nine years the trouble had slowly progressed, with numerous fulminating exacerbations of symptoms and some periods of partial recovery. A proctoscopic and roentgenologic examination in 1924 confirmed the diagnosis of advanced, destructive colitis. At that time treatment with vaccine, prepared from diplostreptococci isolated from the patient's rectal ulcers, was begun, and improvement followed rapidly. The patient gained weight and was soon engaged in a wage-earning occupation. Proctoscopic examinations in 1926 and in January and April 1927 revealed healed colitis. Early in December 1927 there was a slight recurrence, and proctoscopic examination disclosed the typical picture of chronic ulcerative colitis. The

3. Brust, J. C. M., and Borgen, J. A.: The Neoplastic Factor in Chronic Ulcerative Colitis, *New England J. Med.* **210**:692 (March 29) 1934.

# Summary of Data in Twenty-Seven Cases

Case	Year of First Admission	Age on Admission	Chronic Ulcerative Colitis		Time Under Observation at Mayo Clinic	Time from First Symptom to First Examination at Clinic	Time Polypoid Present Before Care-		Age First Ap- pearance, Years	Time from First Symptom to Symptom to Examination	Time from First Symptom to Death	Carcinoma		Basis for Final Diagnosis	Comment
			Time from First Symptom to First Examination	Extent, Grade*	Time from First Symptom to First Examination	Time from First Symptom to First Examination	Time from First Symptom to First Examination	Time from First Symptom to First Examination							
1	1915	9	9 years	4	Yes	21	3 months	Rectum	Proctoscopy and biopsy	From first symptoms to extirpation, nearly 3 months; alive after initial symptom, 7 months					
2	1924	11	8 years	3	Yes	21	5 weeks	Cecum	Biopsy						
3	1925	26	1 year	4	Yes	26	6 weeks	Entire colon	Neeropsy						
4	1933	30	1 week	2	No	30	.....	Rectum	Neeropsy						
5	1927	32	2 months	3	No	32	5 months	Cecum	Resection						
6	1916	19	9 years	3	No	28	6 months	Transverse colon	Biopsy						
7	1927	33	2 years	4	Yes	35	4½ months	Rectum and cecum	Neeropsy						
8	1924	43	2 weeks	3	Yes	43	1 month	Sigmoid and splenic flexure	Biopsy						
9	1910	39	11 years	3	Yes	50	5 months	Rectum (multiple growths)	Resection						
10	1929	47	4 months	3	Yes	47	4 months	Transverse colon	Neeropsy						
11	1917	38	1 year	3	Yes	38	3 months	Splenic flexure and descending colon	Resection						
12	1916	53	1 year	Unknown	Yes	56	.....	Unknown	Neeropsy						
13	1919	43	2 years	3	Yes	43	9 months	Transverse colon	Neeropsy						
14	1922	60	1 day	3	No	60	.....	Sigmoid	Neeropsy						
15	1923	57	2 weeks	3	No	57	.....	Hepatic flexure	Neeropsy						
16	1923	63	8 months	3	Yes	63	.....	Cecum	Neeropsy						
17	1927	55	3 days	Unknown	No	55	.....	Descending colon	Neeropsy						
18	1921	69	3 days	1	No	59	6 weeks	Hepatic flexure	Neeropsy						
19	1919	60	4 weeks	1	No	60	.....	Rectum	Resection						
20	1925	45	3 months	1	Yes	45	3 months	Anus to splenic flexure (multiple growths)	Biopsy						
21	1924	10	2 months	3	No	40	.....	Cecum	Neeropsy						
22	1931	45	1 week	1	Yes	45	.....	Anus to splenic flexure (multiple growths)	Biopsy						
23	1925	65	1 year	1	No	65	.....	Sigmoid	Resection						
24	1932	10	5 years	3	Yes	40	.....	Rectum	Biopsy						
25	1927	32	2 years	3	Yes	34	.....	Rectum	Biopsy						
26	1923	46	1 year	3	Yes	46	.....	Cecum	Resection						
27	1929	53	4 years	1	Yes	57	2½ months	Rectum	Biopsy						

\* Grade 1 indicates involvement of the entire colon and the terminal portion of the ileum; grade 2, the entire colon; grade 3, the anus to the hepatic flexure, and grade 4, the anus to the splenic flexure.

condition grew progressively worse, and proctoscopic examination on Jan. 3, 1928, revealed hyperplasia of the mucosa in several places, with an indurated ridge measuring 2 by 5 cm., about 8 cm. from the anus. A specimen of tissue removed from this region was reported as being adenocarcinoma, grade 4. Radium applied locally caused shrinkage of the lesion and an apparent beneficial effect on the mucosa generally. However, improvement was only temporary; the patient began to fail rapidly and died less than five months after the first appearance of the malignant change.



Fig. 1 (case 20).—Roentgenogram showing chronic ulcerative colitis involving the colon distal to the middescending segment. Examination revealed that this entire segment was densely infiltrated with carcinoma as well.

Data on some of the early cases are not complete, but in eighteen of the twenty-seven cases the entire colon was involved by severe, advanced destructive colitis. In recent years the malignant progress of carcinoma has been graded. In six of these cases the lesion was graded 4; in one, 3, and in five, 2. In cases 3, 9, 20 and 22, the intestines were stiff, carcinomatous tubes as far cephalad as they could be examined (fig. 1). In several other cases multiple disseminated carcinomas were present, and in still others there was chronic ulcerative colitis involving the entire colon associated with a single carcinomatous portion (figs. 2 and 3 and table).





Fig. 2 (case 6).—Roentgenograms showing: *A*, the colon typically involved by chronic ulcerative colitis (taken in 1916); *B*, the carcinomatous defect in the midtransverse colon.



Fig. 3 (case 10).—*A*, photograph of a single carcinoma with chronic ulcerative colitis. *B*, roentgenogram showing a stricture-like defect of the transverse colon near the hepatic flexure.

These statistics suggest a rather hopeless outlook for the patient with chronic ulcerative colitis in whom colonic carcinoma develops. In general, this may be true, but some striking exceptions are to be found. Two of the seven new cases, reports of which have not hitherto been published, are here reported in detail. These are cases 4 and 27 in the table.

#### REPORT OF CASES

CASE 4.—A man, aged 30, came to the clinic on Sept. 15, 1933, complaining of chronic ulcerative colitis of eight years' duration. In July 1925, during his



Fig. 4 (case 4).—Roentgenogram showing chronic ulcerative colitis involving the colon from the anus to the splenic flexure.

first episode of bloody dysentery, he had averaged thirty rectal discharges daily. His weight had gone from 210 to 147 pounds (95.3 to 66.7 Kg.) within eight weeks. The trouble had continued in the main without remission, although there had been short periods of improvement, such as those which occurred in 1932 and 1933, when his weight had reached 188 pounds (85.3 Kg.) and when the bowel movements had become reduced to five or six every twenty-four hours. During this year treatment was for a diplostreptococcic type of colitis. On Sept. 1, 1933, he had had a peculiar intermittent throbbing sensation in the rectum, with a sense of rectal blockage. At that time diarrhea had increased. He had consulted the physician at his home, and proctoscopic examination had revealed carcinoma of the rectum on an inflammatory base.

On admission the patient's general condition was good. The value for hemoglobin was 15.2 mg. per hundred cubic centimeters of blood; the erythrocytes numbered 4,180,000, and the leukocytes, 11,700, per cubic millimeter of blood. Of the leukocytes, 73 per cent were polymorphonuclear neutrophils. A roentgenogram of the thorax showed nothing abnormal. Sigmoidoscopic examination revealed a tube from 1 to 2 cm. in diameter which was contracted for 24 cm. Just above the anus and involving the inner margin of the posterior and left wall of the rectum was an irregular superficial, nodular lesion measuring about 2 by 2 cm. A specimen of tissue revealed adenocarcinoma, grade 2. A roentgenogram dis-



Fig. 5 (case 4).—Photograph of the descending colon and the rectum. The carcinoma may be readily identified in the rectum; the bowel is extensively ulcerated and contracted.

closed evidence of chronic ulcerative colitis distal to the middle of the transverse colon, with extreme narrowing of the distal segments (fig. 4).

The patient was given a short course of treatment with a solution of the specific antibodies and intraperitoneal injections of vaccine made from streptococci and colon bacilli, and on September 22 the abdomen was explored through an upper left rectus incision. There were no hepatic metastatic growths. The right half of the colon seemed normal. The remainder of the colon, beginning just proximal to the splenic flexure, was contracted, thick-walled and ropelike—its appearance being

grossly typical of that in chronic ulcerative colitis. The transverse colon was divided at its median point; the end of the distal segment was closed and covered with omentum, and the distal end of the proximal portion was utilized for the single-barreled type of colostomy. Postoperative convalescence was somewhat stormy because of the development of bilateral parotitis, but this was effectively treated by the use of surface packs of radium. The patient was allowed to return home for a few weeks.

The patient returned to the clinic on November 18. His general condition was much improved, and he had gained 12 pounds (5.4 Kg.). On November 21, the entire portion of the colon distal to the colonic stoma and rectum was removed (fig. 5). Recovery was uneventful. On Feb. 6, 1934, two and one-half months later, the patient reported that his weight and strength were normal and that he had resumed his usual duties as operator of an oil station. A similar report was made five months after operation.

Surgical treatment in this case was a formidable undertaking. A surgical procedure of somewhat less magnitude could have been chosen had we been dealing with a malignant disease only of the rectum, but a malignant process superimposed on an intractable chronically ulcerated bowel presents a different problem. If the diseased segment of bowel is resected in such cases, the result is unsatisfactory, and frequently the patient dies. If a colonic stoma had been made in the descending colon in this case, and if recovery from operation had followed, the result still would have been unsatisfactory. Occasionally a colonic stoma is seen in an extensively ulcerated colon. In these cases the colonic stoma is usually so contracted and small that elimination is inadequate and general debilitation from the disease is not lessened. Obviously, in such cases, another stoma has to be made in healthy bowel proximal to the diseased segment.

In such a case as the foregoing, then, if any surgical procedure is to be carried out, the entire diseased segment should be removed. If only inflammatory disease had been present, obviously an ileostomy or a colostomy alone would have been resorted to, which in some cases of intractable, chronic ulcerative colitis with other complications is sufficient. Occasionally, however, it becomes necessary to remove the diseased colon in such cases because of general debilitation due to the presence of an overwhelming infection.

CASE 27.—An unmarried woman, aged 53, came to the clinic on May 6, 1929, with a history of chronic ulcerative colitis of three years' duration. There had been many bloody purulent rectal discharges. Proctoscopic examination at that time revealed the usual granular, easily bleeding mucous membrane. Diplo-streptococci were isolated from the rectal lesions. The patient was given a solution of the specific antibodies followed by some vaccine; during the succeeding months her improvement was satisfactory. When the colitis began to improve, she mentioned that she had had menorrhagia for a year; dilatation and curettage revealed adenocarcinoma, grade 1, of the fundus of the uterus. On June 1, 1929, total abdominal hysterectomy was performed. Recovery from both procedures

was satisfactory, so that she was able to return to her teaching. She made frequent reports by mail and as late as Aug. 15, 1933, she reported that she was in excellent condition. However, on Jan. 1, 1934, she stated that she had had recurring cramping pain in the left lower abdominal quadrant. The first attack had occurred in November, and by the time of her return to the clinic, on Feb. 1, 1934, she had had five or six attacks suggestive of an obstructive lesion. Digital examination revealed an annular lesion on an inflammatory base, in the lower portion of the sigmoid flexure; this lesion had narrowed the lumen to such an extent that it did not admit the index finger. The walls of the rectum were somewhat fibrous, but more flexible than they had been. A specimen removed from the lesion revealed adenocarcinoma, grade 2. The mucous membrane of the rectum below the lesion appeared normal as viewed through the proctoscope.

On February 6, exploration was made through a left rectus incision. Palpation of the liver did not reveal metastatic growths. The aortic lymph nodes were not palpable. Examination of the entire colon, beginning at the cecum, was carried out. The walls of the bowel were normal to palpation, in contrast to the typically ropelike colon found in ulcerative colitis. Exploration of the pelvic portion of the sigmoid revealed a rounded mass, evidently a carcinoma. The lower borders of the growth extended to within 5 cm. of the pelvic peritoneal fold. The growth was movable. A colonic stoma was made in the middle of the descending colon in anticipation of a second surgical procedure at the time at which the neoplasm was to be resected. Convalescence following this first procedure was satisfactory.

Four weeks later a second operation was carried out through an abdominal incision low in the median line. Segmental resection of the lower portion of the sigmoid was performed, and an end-to-end anastomosis was made (fig. 6). After the procedure was completed, a large rectal tube was passed through the colonic stoma into the distal segment of the bowel, beyond the anastomosis and into the lower portion of the rectum. The immediate convalescence was satisfactory. On the sixth postoperative day the patient's temperature became elevated to 104 F., with marked acceleration of the pulse rate. Death occurred two days later on the eighth postoperative day. Clinically, the cause of death was peritonitis, and this impression was corroborated at necropsy. Distant metastatic growths were not found.

In the last two years one of us (Dr. Dixon) has carried out eight operations of this sort for growths in the lower part of the sigmoid flexure; seven of the patients recovered. Was the presence of long-standing chronic ulcerative colitis a factor which enhanced the development of peritonitis? To any one who has carried out abdominal operations on patients suffering from chronic ulcerative colitis it is apparent that fulminating peritoneal infection is not uncommon, and even though in the case in point there had been marked symptomatic relief from colitis, it seems possible that some residual infection still remained in the wall of the bowel.

Intraperitoneal vaccination carried out preoperatively has reduced the mortality rate from peritonitis appreciably. If peritonitis develops, however, it is usually of an overwhelming type, as it was in this case, and the causative organism is usually a *streptococcus*.

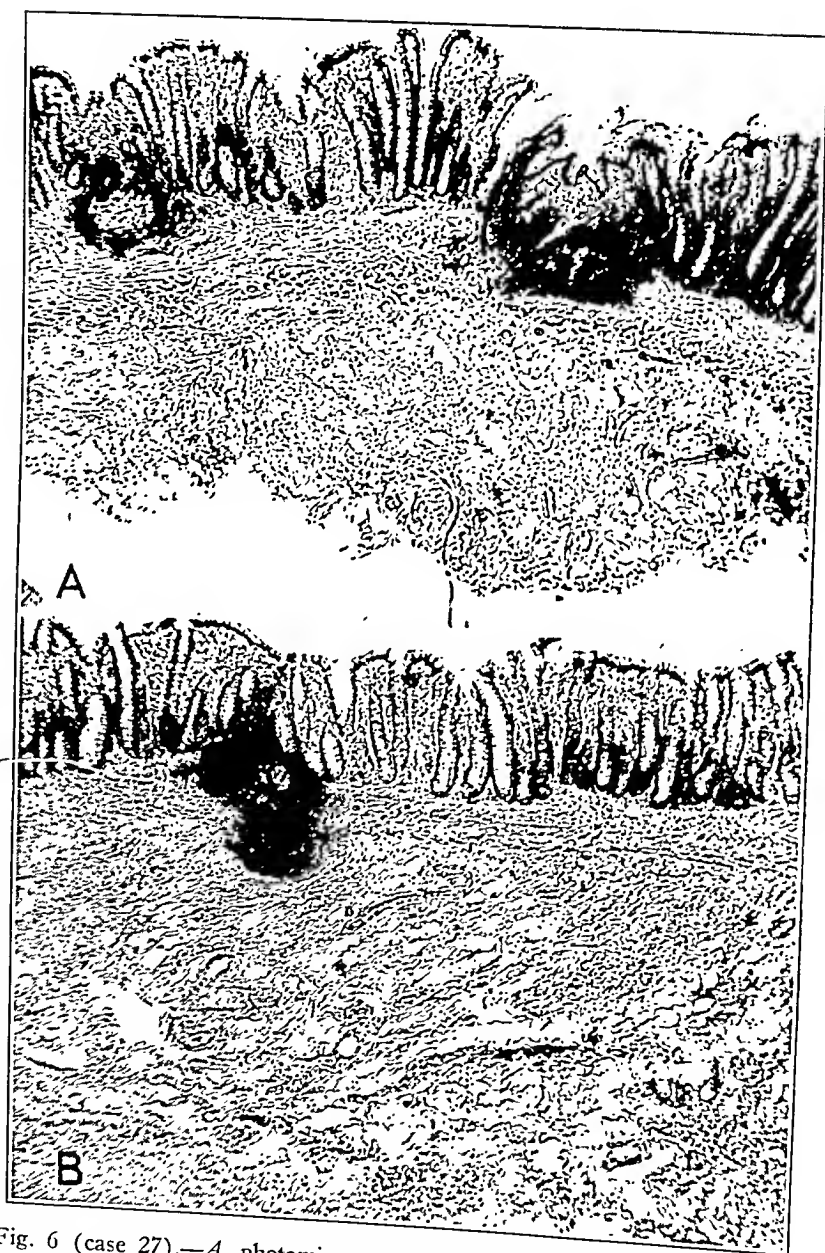


Fig. 6 (case 27).—*A*, photomicrograph of a section of the wall of the colon just above the growth. *B*, photomicrograph of a section of the rectum below the growth. The comparatively adequate wall which resulted after the healing of the chronic ulcerative colitis may be noted.

## COMMENT

So far, no satisfactory treatment for diffuse colonic carcinomatosis, such as was present in cases 3, 9, 20 and 22, is at hand, nor have we any satisfactory treatment for the higher grades of carcinoma associated with this form of colitis. However, for localized, relatively early carcinoma of grades 1 and 2, in cases in which colitis is under fair control, radical extirpation of the diseased colon with the carcinoma offers the patient a good chance of recovery.

It should be stated that in cases 24 and 25 polypoid excrescences in the rectum were fulgurated when the colitis was under control, and this treatment alone has been adequate so far, since the small carcinomas have not recurred. This suggests the importance of prompt proctoscopic observation with any change in symptoms. It also emphasizes the importance of grading specimens removed for biopsy. These two specimens were the only ones in the series recorded as showing malignancy of grade 1.

One is again confronted, and in a most dramatic manner, with the hopelessness, in all probability, of rapidly developing carcinoma among younger persons. In general, in these cases the younger the patient, the more likely it is that the disease will be of the fulminating type and the carcinoma multiple and of a high grade of malignancy.

An attempt to resect the growth locally when active, or even quiescent, colitis is present seems futile. It seems best to resect the entire section of the colon involved by colitis and containing one or more carcinomas. It seems more than accidental that the five surviving patients had adequate treatment with specific antibody solution (concentrated serum) or vaccine prepared from the diplostreptococci of chronic ulcerative colitis, or both, prior to any attempted surgical procedure and that in each case the active stage of colitis was under control when surgical intervention was undertaken. Contrasted with this, only seven of the twenty-two patients who died were given serum or vaccine, and only three of them to the point of control of symptoms. We gained the impression, through close observation, that in these three cases as healing took place the factor responsible for the healing lost control and the mucosa grew wildly as new hyperplastic tissue.

# HEPATIC FUNCTION

## III. THE EFFECT OF CHOLECYSTECTOMY ON HEPATIC FUNCTION

A. CANTAROW, M.D.

E. GARTMAN, M.D.

AND

G. RICCHIUTI, M.D.

PHILADELPHIA

Considerable attention has been directed toward the morphologic changes which occur in the biliary system following surgical removal of the gallbladder. There are, however, practically no data available regarding the effect of cholecystectomy on the functional efficiency of the liver. At first it seems improbable that mere removal of the gallbladder should exert any deleterious effect on hepatic function. However, every surgeon of experience in this field has encountered instances of serious postoperative morbidity and even death following simple cholecystectomy in patients who were apparently in good condition before operation. A variety of factors are involved in the production of many of these postoperative calamities, e. g., anesthesia, undetected hepatic damage, renal complications, operative trauma and shock. In certain cases, however, the most careful preoperative study fails to reveal any significant hepatic or renal functional impairment; cholecystectomy is performed with no undue trauma; anesthesia, general, spinal or local, is apparently free from untoward effects, and still the patient promptly shows evidence of profound functional disturbance, particularly of the liver and kidneys, and may die within a few days after operation.

In an attempt to investigate the pathogenesis of these postoperative phenomena we have been studying patients with disease of the biliary tract before, and at frequent intervals after, operation. In the present report we shall review our observations with regard to the concentration of serum bilirubin and the retention of bromsulphalein in a series of sixty patients with cholecystitis, without clinical jaundice, on whom simple cholecystectomy was performed.

### EXPERIMENTAL DATA

As stated earlier, no patient in this series was clinically jaundiced; gallstones, when present, were confined to the gallbladder. Simple cholecystectomy was performed in each case with the patient under nitrogen monoxide and ether, infiltration or spinal anesthesia. In no case was the common duct manipulated or other operative procedure car-

---

From the Laboratory of Biochemistry, Jefferson Hospital.



ried out. All the patients were in good clinical condition before and during operation, and there were no fatalities.

The serum bilirubin was determined by the quantitative van den Bergh procedure as modified by Thannhauser and Andersen. As stated in a previous report,<sup>1</sup> the normal range of serum bilirubin, according to our experience, is from 0.1 to 1 mg. per hundred cubic centimeters; in about 50 per cent of the persons the serum bilirubin falls below 0.5 mg.,

TABLE 1.—Data for Patients Showing No Preoperative Hyperbilirubinemia or Retention of Dye

Patient	Serum Bilirubin, Mg. per 100 Ce.		Retention of Dye, Percentage	
	Before	After	Before	After
L. F. ....	0.40	0.76	0	0
A. L. ....	0.50	0.90	0	10
A. An. ....	1.00	0.90	0	0
E. Th. ....	0.40	0.26	0	0
L. C. ....	0.62	0.86	0	0
I. B. ....	0.90	1.30	0	0
T. Y. ....	0.72	0.86	0	0
A. S. ....	0.70	1.10	0	10
E. Le. ....	0.85	1.20	0	0
A. Ab. ....	0.80	1.20	0	10
E. Le. ....	0.65	0.84	0	0
J. D. ....	0.57	0.74	0	0
M. M. ....	0.60	0.90	0	10
M. G. ....	0.72	0.98	0	0
T. M. ....	0.48	0.72	0	0
H. MeA. ....	0.48	0.75	0	10
J. C. ....	0.37	0.62	0	0
F. R. ....	0.92	0.90	0	20
A. M. ....	0.36	0.64	0	0
A. DeC. ....	0.60	1.20	0	10
S. S. ....	0.72	0.74	0	10
B. Z. ....	0.52	1.09	0	20
R. H. ....	0.55	0.36	0	30
M. R. ....	0.76	1.40	0	0
J. R. ....	0.52	1.10	0	25
M. K. ....	0.41	0.70	0	10
S. B. ....	0.32	0.40	0	20
A. Ca. ....	0.50	0.50	0	15
S. V. ....	0.65	0.90	0	0
L. V. ....	0.80	0.42	0	0
M. Sm. ....	0.68	0.32	0	0
C. W. ....	0.56	1.08	0	0
M. Sh. ....	0.40	0.60	0	0
M. H. ....	0.39	0.52	0	0
S. B. ....	0.35	0.65	0	0
L. C. ....	0.11	0.12	0	0
S. R. ....	0.30	0.60	0	20
C. M. ....	0.70	0.60	0	50
M. M. ....	0.43	0.23	0	0
A. K. ....	0.80	0.36	0	0
C. C. ....	0.68	0.46	0	0

and in about 95 per cent it fell below 0.8 mg. Bromsulphthalein was administered in the dosage of 2 mg. per kilogram of body weight, the degree of retention being determined at the end of thirty minutes.

Several studies were made in the majority of instances; the two figures reported here are those obtained within twenty-four hours before and twenty-four hours after cholecystectomy. No morphine was administered to any patient in this series between the time of operation and the reported postoperative observations.

1. Cantarow, A.: Hepatic Function: I. Noncalculous and Calculous Cholecystitis, Arch. Int. Med. 54:540 (Oct.) 1934.

In order to simplify the analysis of the experimental data, the patients may be divided into several groups in accordance with observations made before operation.

*Patients with No Preoperative Hyperbilirubinemia or Retention of Dye.*—There were forty-one patients who before operation showed neither hyperbilirubinemia nor retention of bromsulphalein after thirty minutes. The detailed findings are presented in table 1. A significant increase in the concentration of serum bilirubin twenty-four hours after

TABLE 2.—Data for Patients Showing Preoperative Hyperbilirubinemia or Retention of Dye

Patient	Serum Bilirubin, Mg. per 100 Cc.		Retention of Dye, Percentage	
	Before	After	Before	After
M. R. ....	2.00	1.20	10	10
R. M. ....	0.65	0.70	5	0
M. C. ....	0.90	1.40	5	10
E. F. ....	0.50	1.60	10	20
P. S. ....	0.70	0.55	5	15
M. P. ....	0.70	0.92	5	20
J. A. ....	0.50	0.92	25	60
J. M. ....	0.70	0.75	5	0
F. C. ....	2.40	0.50	0	0
E. T. ....	0.50	0.40	100	5
F. G. ....	1.20	0.50	0	10
M. L. ....	1.10	0.58	0	10
J. R. ....	1.10	2.24	0	15
T. F. ....	1.36	1.26	15	0
A. Cu. ....	0.44	3.76	5	30
L. A. ....	1.20	0.10	0	0
E. M. ....	2.24	0.63	45	5
M. L. ....	2.40	3.60	15	55
J. H. ....	0.75	0.92	5	10

TABLE 3.—Summary of Data for Patients with No Preoperative Retention of Dye

Cases	Serum Bilirubin				Retention of Dye		
	Before, Mg. per 100 Cc.	After, Mg. per 100 Cc.	Increased	Decreased	Before	After	Increased
46	0.11-2.40	0.12-2.24	27 (60%)	13 (28%)	0	0-50	19 (41%)

cholecystectomy occurred in twenty-six cases (63.4 per cent), the value being above the upper limit of normal (1 mg.) in nine instances (21.9 per cent). An abnormal degree of retention of dye (from 10 to 50 per cent) was noted twenty-four hours after operation in sixteen cases (39 per cent).

There was no apparent relation between the postoperative increase in serum bilirubin and the retention of dye. Of the sixteen patients in whom retention of dye occurred, two showed decrease in the concentration of serum bilirubin (R. H. and C. M., table 1). Furthermore, these two patients exhibited the most marked degree of retention of dye observed in this group (30 and 50 per cent). In five instances reten-

tion of dye was accompanied by no significant alteration in the degree of bilirubinemia.

*Patients with Preoperative Hyperbilirubinemia or Retention of Dye.*—There were nineteen patients who showed some degree of either hyperbilirubinemia or retention of dye before operation. The detailed findings are presented in table 2. Since the significant findings in this group will be referred to later, it is not necessary to review them at this point; we merely point out again the apparent lack of consistent correlation between the degree of bilirubinemia and the retention of dye.

TABLE 4.—*Summary of Data for Patients with Preoperative Retention of Dye*

Cases	Serum Bilirubin				Retention of Dye			
	Before, Mg. per 100 Cc.	After, Mg. per 100 Cc.	Increased	Decreased	Before	After	Increased	Decreased
14	0.44-2.40	0.40-3.76	8 (57%)	4 (28%)	5-100	0.55	8 (57%)	2 (36%)

TABLE 5.—*Summary of Data for Patients with No Preoperative Hyperbilirubinemia*

Cases	Serum Bilirubin				Retention of Dye			
	Before, Mg. per 100 Cc.	After, Mg. per 100 Cc.	Increased	Decreased	Before	After	Increased	Decreased
51	0.11-1.00	0.12-3.76	33 (66%)	10 (20%)	0-100	0.50	23 (45%)	3 (6%)

TABLE 6.—*Summary of Data for Patients with Preoperative Hyperbilirubinemia*

Cases	Serum Bilirubin				Retention of Dye			
	Before, Mg. per 100 Cc.	After, Mg. per 100 Cc.	Increased	Decreased	Before	After	Increased	Decreased
9	1.10-2.40	0.50-3.60	2 (22%)	7 (78%)	0-45	0.55	4 (44%)	2 (22%)

*Patients with No Preoperative Retention of Dye.*—There were forty-six patients with no retention of bromsulphalein before operation. The detailed findings in this group are presented in table 3. It will be noted that a postoperative increase in bilirubinemia occurred in twenty-seven cases (60 per cent) and retention of dye in nineteen cases (41 per cent).

*Patients with Preoperative Retention of Dye.*—There were fourteen patients in whom retention of dye (from 5 to 100 per cent) was present before operation. The detailed findings are presented in table 4. A postoperative increase in the bilirubin content of the blood occurred in eight cases (57 per cent); an increase in the degree of retention of dye in eight cases (57 per cent), and a decrease in the retention of dye in five cases (36 per cent).

*Patients with No Preoperative Hyperbilirubinemia.*—There were fifty-one patients in whom the concentration of serum bilirubin was within normal limits before operation. The detailed findings are presented in table 5. The concentration of serum bilirubin increased following operation in thirty-three cases (66 per cent), and the degree of retention of dye increased in twenty-three cases (45 per cent) and decreased in three cases (6 per cent).

*Patients with Preoperative Hyperbilirubinemia.*—There were nine patients with preoperative hyperbilirubinemia. The detailed findings are presented in table 6. A postoperative increase in the concentration of serum bilirubin occurred in two (22 per cent), and a decrease in seven (78 per cent); a postoperative increase in the degree of retention of dye occurred in four cases (44 per cent), and a decrease in two (22 per cent).

#### COMMENT

As was stated earlier, hyperbilirubinemia and retention of bromsulphalein eventually disappeared in every case in this series, although in some instances one or the other persisted for as long as four days. Retention of dye usually persisted longer than hyperbilirubinemia in cases in which both were present twenty-four hours after operation.

The question naturally arises as to why even temporary impairment of the excretory function of the liver should occur following cholecystectomy. The possible influence of anesthesia is obviously of importance. Chloroform was not employed for any patient in this group, nor was avertin, which, according to Bourne and Raginsky,<sup>2</sup> may cause increased retention of bromsulphalein in the presence of hepatic damage. There seems to be little doubt that ether has a distinct effect on certain hepatic functions. A moderate diminution in the glycogen content of the liver following ether anesthesia was reported by Evans, Tsai and Young<sup>3</sup> and by Macleod and Pearce.<sup>4</sup> A rise in venous blood sugar during and after the administration of ether has been demonstrated by a number of investigators, including Mekie and Miller,<sup>5</sup> Mackay,<sup>6</sup> Ross and Davis,<sup>7</sup>

2. Bourne, W., and Raginsky, B. B.: Effect of Avertin upon the Normal and Impaired Liver, *Am. J. Surg.* **14**:653, 1931.

3. Evans, C. L.; Tsai, C., and Young, F. G.: The Behavior of Liver Glycogen in Experimental Animals, *J. Physiol.* **73**:67, 1931.

4. Macleod, J. J. R., and Pearce, R. G.: Studies in Experimental Glycosuria: VI. The Distribution of Glycogen Over the Liver Under Various Conditions, *Am. J. Physiol.* **27**:341, 1911.

5. Mekie, E., and Miller, H.: Effects of Anesthesia, Operation and Certain Other Factors on Glycemia, *Brit. M. J.* **1**:244, 1929.

6. Mackay, R. L.: Atypical Case of Hyperglycemia in General Anesthesia, *Brit. M. J.* **1**:892, 1928.

7. Ross, E. L., and Davis, L. H.: The Rôle of the Pancreas in Hyperglycemia from Ether, *Am. J. Physiol.* **53**:391, 1920.

Mahler<sup>8</sup> and Cantarow and Gehret.<sup>9</sup> This ether hyperglycemia is generally attributed to increased hepatic glycogenolysis.

Although the importance of the hepatic glycogen content to the maintenance of hepatic function and to the capacity of the liver for resisting injury is well recognized, the metabolic functions of the liver, glycogenesis and glycogenolysis, at least, are more seriously affected by ether than are its excretory functions. In marked contrast to their observations following the administration of chloroform, Rosenthal and Bourne<sup>10</sup> noted only slight and transient retention of bromsulphalein following ether anesthesia for periods of from one-half to two hours. The average retention in the latter instance was 14 per cent (fifteen minute retention), normal values being invariably obtained within twenty-four hours. On the other hand, Rathery and Saison<sup>11</sup> reported degenerative hepatic lesions following prolonged ether anesthesia in animals, and in thirty-eight cases Chevrier<sup>12</sup> noted hyperbilirubinemia, which was greater in degree but much more transient than that following the administration of chloroform. Quénu, Duval and Brulé<sup>13</sup> also reported the presence of urobilinuria in several cases. However, the observations of the French investigators are not corroborated by those of the majority of workers in this field and are not in accord with our experimental and clinical findings. Ether appears to exert a distinct effect on the flow of bile, to which reference will be made later.

The work of Rosenthal and Bourne<sup>10</sup> indicated that nitrogen monoxide in the quantities administered to patients in this series produces no demonstrable impairment of hepatic function. Although the preoperative administration of morphine may cause transitory retention of bromsulphalein this effect, as demonstrated by Rosenthal and Bourne<sup>10</sup> and as observed by us, invariably disappears within from twelve to twenty-four hours. No such effect has been noted following anesthesia produced by infiltration of procaine hydrochloride or spinal anesthesia. It appears, therefore, that so far as direct hepatotoxic action

---

8. Mahler, A.: Blood Cholesterol During Ether Anesthesia, *J. Biol. Chem.* **69**:653, 1926.

9. Cantarow, A., and Gehret, A. M.: Ether Hyperglycemia, with Especial Reference to Hepatic Disease, *J. A. M. A.* **96**:939 (March 21) 1931.

10. Rosenthal, S. M., and Bourne, W.: Effect of Anesthetics on Hepatic Function, *J. A. M. A.* **90**:377 (Feb. 4) 1928.

11. Rathery, F., and Saison, M.: Influence nocive de l'éther en inhalation sur le foie et le rein, *Tribuna méd.* **43**:245, 1910.

12. Chevrier, L.: Etudes sur la cholémie post-anesthésique et sur les moyens de la modifier, *Bull. et mém. Soc. de chir. de Paris* **45**:735, 1919.

13. Quénu, E.; Duval, P., and Brulé, M.: Etudes sur la cholémie, post-anesthésique et sur les moyens de la modifier, *Bull. et mém. Soc. de chir. de Paris* **45**:833, 1919.

is concerned, anesthesia played a relatively unimportant part in the production of the observed postoperative changes in bilirubinemia and excretion of dye. This is further borne out by the fact that there was no correlation between the type or duration of anesthesia and either the incidence or the severity of the postoperative changes.

Several observers have described the effects of cholecystectomy on the flow of bile. The work of Rous and McMaster,<sup>14</sup> McMaster and Elman<sup>15</sup> and many others during the past thirteen years indicates that the chief demonstrable functions of the gallbladder are the concentration and storage of bile. By virtue of these functions the relatively large volume of bile which is being excreted continually by the liver is diminished (to one-sixth or one-eleventh its original volume), and the continuous flow from the liver is converted into an intermittent flow into the duodenum in accordance with physiologic demands for the presence of bile in the digestive mixture. One would expect removal of the gallbladder to result in well defined changes in the flow of bile. The influence of ether anesthesia in this connection cannot be disregarded. Mann<sup>16</sup> showed that the flow of bile was distinctly diminished in dogs during ether anesthesia, although no changes could be demonstrated in the liver. McMaster, Broun and Rous<sup>17</sup> confirmed this observation, noting in addition that the bile was highly concentrated and deeply pigmented, which would cast doubt on the probability of the existence of marked hepatic functional impairment, at least so far as the excretion of bile pigment is concerned. Diminution in, or at times complete cessation of, bile flow during operations on the bile passages under ether anesthesia has been noted, among others, by Nielson and Meyer,<sup>18</sup> Wertheimer<sup>19</sup> and Hooper and Whipple.<sup>20</sup>

As stated earlier, McMaster, Broun and Rous<sup>17</sup> found that during the first few days after cholecystectomy and intubation of the common duct the bile flow was almost invariably scanty, syrupy in consistency

---

14. Rous, P., and McMaster, P. D.: The Concentrating Activity of the Gallbladder, *J. Exper. Med.* **34**:47 (July) 1921.

15. McMaster, P. D., and Elman, R.: Studies on Urobilin: Physiology and Pathology, *J. Exper. Med.* **41**:513, 1925.

16. Mann, F. C.: Investigations of the Relation of Anesthesia to Hepatic Function, *Anesth. & Analg.* **4**:107, 1925.

17. McMaster, P. D.; Broun, G. O., and Rous, P.: Studies on the Total Bile: I, *J. Exper. Med.* **37**:395, 1923.

18. Nielson, N. M., and Meyer, K. F.: The Reaction and Physiology of the Hepatic Duct and Cystic Bile of Various Laboratory Animals, *J. Infect. Dis.* **28**: 510 (May-June) 1921.

19. Wertheimer, E.: Sur la circulation entéro-hépatique de la bile, *Arch. Physiol. norm. et path.* **4**:577, 1892.

20. Hooper, C. W., and Whipple, G. H.: Bile Pigment Metabolism: I. Bile Pigment Output and Diet Studies, *Am. J. Physiol.* **40**:332, 1916.

and deeply pigmented. Not until after from three to seven or more days did the volume of the flow reach the quantity yielded during the succeeding weeks. McMaster attributed this phenomenon largely to the effect of the operation on the liver, although the low intake of food may have been a contributory factor. By direct observation Puestow<sup>21</sup> found that cholecystectomy has a definite and constant effect on the flow of bile into the duodenum. Whereas with the gallbladder intact there is no flow into the intestine during fasting, in the cholecystectomized animal there is a constant flow under low pressure, the orifice of the common duct being almost always open. Furthermore, in the absence of the gallbladder, the stimulating influence of food on the flow of bile was found to be almost absent during the period before physiologic compensation was established. It is probable also that this abnormal, almost continuous flow of small quantities of bile into the duodenum further diminishes the stimulus to secretion of bile by the liver, which is normally supplied by reabsorption of relatively large quantities of bile acids periodically discharged into the duodenum.

Under normal conditions the quantity of bile pigment excreted by the liver in twenty-four hours is remarkably constant. The studies of Greene and Snell<sup>22</sup> indicated that the liver is normally able to secrete bile of a widely varying concentration of bilirubin (from 20 to 1,000 mg.). They stated that increased excretion of bilirubin in the bile is brought about primarily by an increase in the concentration of the pigment, although when excessive amounts are present there may be an additional increase in the volume of the output. Comparatively little is known regarding the factors which determine the elimination of bilirubin in the presence of hepatic disease. However, we have at hand experimental evidence which, with clinical observations, suggests that in the presence of functional impairment the liver, just like the kidney, loses its power of concentration, and, as in renal disease, the required quantity of solids can be excreted only by increasing the volume of fluid eliminated simultaneously. Choleresis in hepatic disease, therefore, may be regarded as an effort to compensate for diminution in the concentrating power of the liver, being analogous to the polyuria of early renal functional impairment in chronic glomerulonephritis. Under such circumstances any factor which tends to diminish the volume of bile would increase the tendency toward retention in the blood of those substances which can no longer be excreted in high concentration. Among these are bilirubin and perhaps bromsulphalein.

---

21. Puestow, C. B.: The Discharge of Bile into the Duodenum: An Experimental Study, *Arch. Surg.* **23**:1013 (Dec.) 1931.

22. Greene, C. H., and Snell, A. M.: Studies in the Metabolism of the Bile: II. The Sequence of Changes in the Blood and Bile Following the Intravenous Injection of Bile or Its Constituents, *J. Biol. Chem.* **78**:691, 1928.

In the light of previous studies reported by one of us,<sup>23</sup> as well as by Judd,<sup>24</sup> Graham and his associates,<sup>25</sup> Tietze and Winkler<sup>26</sup> and many others, it is probable that some diminution in the hepatic functional reserve, if not actual organic hepatic disease, is present in a large proportion of persons with chronic disease of the biliary tract. When in the presence of diminution in the concentrating ability of the liver cholecystectomy is performed, increased retention of bilirubin and bromsulphalein may conceivably result from the sudden consequent diminution in the volume of the flow of bile.

Naturally, in addition to the nature and duration of the anesthesia, such factors as the preoperative state of hepatic function and the extent of operative manipulation are of importance in determining the degree of postoperative hepatic functional impairment. However, analysis of the data obtained in the present series of cases reveals no consistent

TABLE 7.—*Summary of Data for Patients with Patent Cystic Duct*

Cases	Retention of Dye		Serum Bilirubin	
	Increased	Decreased	Increased	Decreased
34	25 (73%)	0	27 (79%)	4 (12%)

TABLE 8.—*Summary of Data for Patients with Nonpatent Cystic Duct*

Cases	Retention of Dye		Serum Bilirubin	
	Increased	Decreased	Increased	Decreased
26	2 (17%)	5 (19%)	8 (31%)	13 (50%)

relationship between these factors and the postoperative functional changes. The factor which appeared to be of significance in this connection was that of obstruction of the cystic duct, as demonstrated by cholecystography or at operation. The detailed data bearing on this point are presented in tables 7 and 8. It will be noted that cholecystec-

23. Cantarow, A.: The van den Bergh Reaction and the Bromsulphalein Test in the Estimation of Hepatic Functional Impairment, *Am. J. M. Sc.* **184**:228, 1932; footnote 1.

24. Judd, E. S.: Relation of the Liver and the Pancreas to Infection of the Gallbladder, *J. A. M. A.* **77**:197 (July 16) 1921. Judd, E. S.; Nickel, A. C., and Wellbrock, W. L. A.: The Association of the Liver in Disease of the Biliary Tract, *Surg., Gynec. & Obst.* **54**:13, 1932.

25. Graham, E. A.: Hepatitis; a Constant Accompaniment of Cholecystitis, *Surg., Gynec. & Obst.* **26**:521, 1918. Peterman, M. G.; Priest, W. S., Jr., and Graham, E. A.: Association of Hepatitis with Experimental Cholecystitis and Its Bearing on the Pathogenesis of Cholecystitis in the Human, *Arch. Surg.* **2**:92 (Jan.) 1921.

26. Tietze, A., and Winkler, K.: Die Beteiligung des Leberparenchyms an der Gallensteinkrankheit, *Arch. f. klin. Chir.* **129**:1, 1924.



tomy was followed by an increase in the degree of retention of dye in twenty-five (73 per cent) of the thirty-four patients in whom the cystic duct was patent, as compared with two (17 per cent) of the twenty-six patients in whom the cystic duct was not patent. Increased bilirubinemia was observed in 79 per cent of the former group as compared with 31 per cent of the latter.

The probable explanation for this difference appears rather obvious. In persons with obstruction of the cystic duct, the biliary passages had been completely deprived of the functional activity of the gallbladder for some time prior to its removal; compensatory changes had occurred, as described by Puestow,<sup>21</sup> and cholecystectomy resulted in practically no further disturbance in the flow of bile. In patients with a patent cystic duct, the gallbladder, although not functioning normally, nevertheless carried a variable portion of the burden which, following its removal, was suddenly thrown on the hepatic and common ducts. This resulted in changes qualitatively if not quantitatively comparable to those which follow experimental cholecystectomy, as reviewed earlier.

#### SUMMARY

Determinations of serum bilirubin and retention of bromsulphalein were made before and after cholecystectomy in sixty patients with cholecystitis without obstruction of the common bile duct.

A temporary increase in serum bilirubin occurred in twenty-six (63.4 per cent) of forty-one patients with apparently normal preoperative hepatic function. Postoperative retention of dye was noted in sixteen (39 per cent) patients in this group.

Increased bilirubinemia occurred in nine (47.3 per cent) and increased retention of dye in eleven (57.9 per cent) of nineteen patients who showed some degree of hyperbilirubinemia or of retention of dye before operation.

This temporary postoperative impairment of hepatic excretory function bore no constant relation to the nature or duration of anesthesia or to the preoperative state of hepatic function in this group of patients. It is believed to be dependent probably on the decrease in the volume of the flow of bile which follows cholecystectomy and which interferes with the mechanism whereby a damaged liver compensates for impairment in its ability to concentrate certain solid constituents of the bile.

Patency or occlusion of the cystic duct appeared to be of significance in determining the occurrence of these postoperative functional abnormalities. Increased retention of dye occurred in 73 per cent and increased bilirubinemia in 79 per cent of the patients with patent cystic ducts, whereas the corresponding figures for the group with obstruction of the cystic duct were 17 and 31 per cent.

# EFFECT OF JEJUNAL FEEDING ON GASTRIC ACIDITY

A. A. APPELL, M.D.

TORONTO, CANADA

In recent years jejunal feeding has been recommended for the treatment of complicated peptic ulcer. Occasionally at operation for ulcer the inflammatory reaction is found to be so intense as to make any extensive surgical procedure unsafe. Some patients have undergone jejunostomy as a palliative measure to maintain them until a more extensive operation could be performed and under such management have improved clinically. Another method of treatment has been to pass a long catheter through the nose or mouth down to the jejunum and to feed the patient through the tube for a period of from four to six weeks. Patients who had not improved with other forms of treatment were said to have improved under this management. Since the acid secretion of the stomach is so intimately concerned with the treatment of peptic ulcer, any method of lowering this secretion would be of some value in the treatment of ulcer. Jejunal feeding is said to lower the acidity of the gastric content. Accordingly, the present experimental study was undertaken to see what effect feeding through a jejunal fistula would have on the reaction of the gastric content.

There are three stimuli which can cause the gastric mucosa to secrete: (1) the sight, smell or taste of food, (2) the presence of certain foods in the stomach and (3) the presence of certain food substances in the intestine. It is with the third mechanism that the research reported here was primarily concerned.

Pavlov<sup>1</sup> noted an intestinal phase of gastric secretion. He found that the introduction of food substances into the duodenum was followed by secretion of gastric juice. Following his observation a series of reports was published in which was described the stimulating effect on gastric secretion of each of a large variety of food substances when introduced into the intestine. Outstanding among these investigations were those reported by Gross,<sup>2</sup> Ivy and Whitlow,<sup>3</sup> Chittenden, Mendel and

---

An abridgment of a thesis submitted to the faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Surgery. The work was done at the Institute of Experimental Medicine, the Mayo Clinic.

1. Pavlov, I. P.: *The Work of the Digestive Glands*, ed. 2, London, Charles Griffin and Company, 1910.

2. Gross, W.: *Beitrag zur Kenntnis der Sekretionsbedingungen des Magens nach Versuchen am Hund*, *Arch. f. Verdauungskr.* **12**:507, 1906.

3. Ivy, A. C., and Whitlow, J. E.: *The Gastrin Theory Put to Physiological Test*, *Am. J. Physiol.* **60**:578 (May) 1922.

Jackson,<sup>4</sup> Edkins and Tweedy<sup>5</sup> and Kauders and Porges.<sup>6</sup> Many of the results reported were contradictory, but on the whole it was generally conceded that gastric secretion was stimulated when food was introduced into the duodenum. Ivy and his co-workers<sup>7</sup> attempted to obtain more accurate results by carefully controlled experiments, and they found that some foods when introduced into the intestine stimulated more gastric secretion than did others. Einhorn<sup>8</sup> applied this knowledge clinically and treated patients who had peptic ulcer by feeding them through a tube introduced into the duodenum; he reported good results. Friedenwald and Wiest<sup>9</sup> also reported cases in which similar treatment was employed. Levy<sup>10</sup> performed a fractional analysis of the gastric content of patients who were receiving duodenal alimentation and found a definite rise in gastric acidity in spite of the clinical improvement. Garbat<sup>11</sup> obtained similar results and studied the problem in more detail, establishing the fact that acid gastric secretion was stimulated by the duodenal feeding of patients with peptic ulcer.

In an attempt to prevent the stimulation of gastric secretion, Bockus<sup>12</sup> fed patients who had ulcer through a tube placed in the jejunum, and found that after this treatment, when the ulcer was healing, gastric acidity was reduced. Henning<sup>13</sup> studied the problem in detail, introducing many food substances into the jejunum to determine

---

4. Chittenden, R. H.; Mendel, L. B., and Jackson, H. C.: A Further Study on the Influence of Alcohol and Alcoholic Drinks upon Digestion, with Special Reference to Secretion, *Am. J. Physiol.* **1**:164 (March) 1898.

5. Edkins, J. S., and Tweedy, M.: The Natural Channels of Absorption Evoking the Chemical Mechanism of Gastric Secretion, *J. Physiol.* **38**:263 (March 22) 1909.

6. Kauders, F., and Porges, O.: Der Einfluss des Duodenalinalhaltes auf die Magensekretion, *Wien. klin. Wchnschr.* **35**:838 (Oct. 26) 1922.

7. Ivy, A. C.; Lim, R. K. S., and McCarthy, J. E.: II. The Intestinal Phase of Gastric Secretion, *Quart. J. Exper. Physiol.* **15**:55, 1925. Ivy, A. C., and McIlvain, G. B.: Excitation of Gastric Secretion by Application of Substances to the Duodenal and Jejunal Mucosa, *Am. J. Physiol.* **67**:124 (Dec.) 1923.

8. Einhorn, M.: A Case of Perforation of the Duodenum Treated Successfully by Duodenal (Jejunal) Alimentation, *M. Rec.* **94**:927 (Nov. 30) 1918; Duodenal Alimentation, *ibid.* **78**:92 (July 16) 1910; Results of Duodenal Alimentation in Peptic Ulcers, *ibid.* **96**:95 (July 19) 1919.

9. Friedenwald, J., and Wiest, P. F.: Some Observations on Duodenal Alimentation, *New York M. J.* **117**:655 (June 6) 1923.

10. Levy, M. D.: The Fractional Estimation of the Gastric Contents During Duodenal Alimentation, *Texas State J. Med.* **16**:483 (March) 1921.

11. Garbat, A. L.: Gastric Secretion in Response to Duodenal Feeding, *Arch. Int. Med.* **32**:771 (Nov.) 1923.

12. Bockus, H. L.: Jejunal Alimentation in Treatment of Peptic Ulcer, *J. A. M. A.* **82**:351 (Feb. 2) 1924.

13. Henning, N.: Untersuchungen über die duodenale und jejunale Ernährung. I. Einfluss der duodenalen und jejunalen Ernährung auf die Nüchternsekretion, *Arch. f. Verdauungskr.* **41**:321 (Dec.) 1927.

their effects on gastric secretion, and found that the food substances which stimulated gastric secretion when given by duodenum did not do so when given by jejunum. Later, with Morawitz,<sup>14</sup> he reported beneficial effects of jejunal feeding through a long catheter in cases of peptic ulcer. Rehder,<sup>15</sup> Gutzeit<sup>16</sup> and Mouzon<sup>17</sup> obtained clinical improvement in cases of ulcer by means of jejunal feeding.

Jejunostomy for jejunal feeding in cases of complicated peptic ulcer has been recommended by many authors. Outstanding among them were Heyd,<sup>18</sup> Walker<sup>19</sup> and Laméris.<sup>20</sup> They found that inoperable ulcers often healed completely, or at least to such an extent that radical operation at a subsequent date could be performed with lessened risk. Scott and Ivy<sup>21</sup> found that most diets used in jejunal feeding were successful if used only for a few weeks. After this time most foods proved to be irritating to the small intestine. Accordingly, they prepared a diet which lowered gastric secretion when fed by jejunum and which could be administered over long periods to dogs without any evidence of irritation. Mensing<sup>22</sup> gave this diet through a jejunostomy tube to his patients who had ulcer and obtained good clinical results.

#### METHOD OF PROCEDURE

In this study an attempt was made to determine what effect jejunal feeding would have on the secretory activity of the stomach. Gastric and jejunal fistulas were made in dogs, the intestinal loop type of fistula as described by Mann and Bollman being used.<sup>23</sup> The jejunal fistulas were placed approximately from 10 to 20 cm. from the ligament of Treitz. All of the operations were performed with the animals under ether anesthesia, and a sterile technic was employed.

14. Morawitz, P., and Henning, N.: Ueber jejunale Ernährung, *Klin. Wchnschr.* 8:681 (April 9) 1929.

15. Rehder, R.: Ulkusbehandlung mit der jejunalen Ernährung im Privathaus, *Med. Welt* 3:1728 (Nov. 30) 1929.

16. Gutzeit, K.: Ueber die Beeinflussung der Magenreiz- und Nüchternsekretion durch Dünndarmverweilsonden sowie durch duodenale und jejunal Nahrungszufuhr, *Ztschr. f. d. ges. exper. Med.* 73:48, 1930; Ueber die therapeutischen Erfolge der duodenalen bzw. jejunalen Ernährung bei Magenkranken, *München. med. Wchnschr.* 77:446 (March 14) 1930.

17. Mouzon, J.: L'alimentation jéjunale dans le traitement des ulcères peptiques, *Presse méd.* 39:37 (Jan. 10) 1931.

18. Heyd, C. G.: Jejunostomy, *Am. J. Surg.* 1:188 (Oct.) 1926.

19. Walker, I. J.: Jejunostomy, *Boston M. & S. J.* 186:108 (Jan. 26) 1922.

20. Laméris, H. J.: Zur Behandlung des Magengeschwürs, *Deutsche Ztschr. f. Chir.* 189:1, 1924.

21. Scott, H. G., and Ivy, A. C.: Jejunal Alimentation: An Experimental Study in Dogs, *Ann. Surg.* 93:1197 (June) 1931.

22. Mensing, E. H.: Treatment of Certain Cases of Duodenal Ulcer by Jejunostomy, *Am. J. Surg.* 15:105 (Jan.) 1932.

23. Mann, F. C., and Bollman, J. L.: A Method for Making a Satisfactory Fistula at Any Level of the Gastro-Intestinal Tract, *Ann. Surg.* 93:794 (March) 1931.

The routine established in making observations was as follows:

1. Each dog was given a mixture of milk and syrup (10 per cent syrup in the whole milk) by mouth three times daily in sufficient amount to supply the necessary fluid and caloric requirement. Specimens of gastric content were withdrawn every hour for a period of eight hours. The  $p_{\text{H}}$ , free acidity and total acidity were determined. The  $p_{\text{H}}$  value of the gastric juice was obtained by the quinhydrone method, and the titrations for the acid values were made with a tenth-normal solution of sodium hydroxide, 1 per cent phenolphthalein and a 0.5 per cent alcoholic solution of dimethyl-amino-azobenzene being used as indicators. A rough measure of the amount of secretion was also noted. The mixture of milk and syrup was selected because it was always available, being used as a routine for postoperative feeding, and because the dogs had maintained their weight and general condition when fed this mixture over a period of several months. When constant readings were obtained, the mixture was fed by jejunum three times daily, and following this it was again given by mouth as a check on the first set of readings. The dogs were made to fast for at least eighteen hours before each set of experiments.

2. The dogs were then given five feedings daily by mouth, then by jejunum, and then again by mouth, as before. The total number of cubic centimeters of milk and syrup used was the same for each dog per day.

3. In order to determine whether or not an intestinal fistula connected with the stomach would have any effect on the gastric  $p_{\text{H}}$  and acidity, three dogs were used which had no gastric fistula but only an intestinal fistula, the specimens of gastric juice being withdrawn by means of a stomach tube. Two dogs which had only a duodenal fistula were used for a study of the  $p_{\text{H}}$  of the duodenal content following feeding of the same mixture of milk and syrup three and five times daily.

4. In order to determine whether or not some of the secretion was due to psychic stimulation, although great care was exercised in all experiments to prevent this, two dogs were given sodium amytal by jejunum in doses sufficient to produce sleep, and determinations were made as before.

5. Some of the simpler food substances were tested to determine whether or not a nonstimulating food could be found. The dogs fasted, then the individual food substances were given by jejunum, gastric juice was withdrawn at intervals of half an hour for from three to four hours, and the usual determinations were made. At least two dogs were used for each food substance tested, and readings were obtained for at least two days. The following substances were used: casein, 2 Gm. per kilogram; butter, 1 Gm. per kilogram; cream, 3 cc. per kilogram; cottonseed oil, 3 cc. per kilogram; sucrose, 2 Gm. per kilogram; dextrose, 2 Gm. per kilogram; flour, 2 Gm. per kilogram; eggs, approximately one per 10 kilograms; peptone, 2 Gm. per kilogram; Liebig's meat extract, 1 Gm. per kilogram; glycine, 1 Gm. per kilogram, and the special diet devised by Ivy.

## RESULTS

*Amount of Secretion.*—In general, more secretion was withdrawn from the stomach when the milk was fed by jejunum than when it was fed by mouth. In the two dogs which had only a jejunal fistula and from which the gastric content was withdrawn by stomach tube, there was no appreciable difference in the amount of secretion obtained whether they were fed by mouth or by jejunum, probably because the

stomach tube was less efficient than the catheter inserted through a fistula in withdrawing the gastric content. Furthermore, there was a greater amount of secretion when five feedings were given daily than when only three feedings were given, even though the total number of cubic centimeters of the milk mixture was the same in each case.

*Hydrogen Ion Concentration of the Gastric Content.*—Lower values for the  $p_H$  of the gastric content were obtained with jejunal feedings than with oral feedings, and these values were appreciably lower when five feedings were given daily than when three feedings were given daily.

*Free Acidity of the Gastric Content.*—There was little or no free acid in the gastric content with oral feeding, but a moderate amount was present with jejunal feeding. Occasionally the free acidity reached a high level. Moreover, the free acidity reached a higher level when five feedings were given daily than when three feedings were given daily.

*Average Maximal Acidity of the Gastric Content Following the Jejunal Feeding of Various Food Substances*

Food Substance Used	$p_H$	Free Acid*	Total Acid*
Sucrose	5.91	2.5	13
	5.14	2.5	25
	4.68	4.0	25
Flour	4.77	5.0	26
Eggs	5.35	5.0	22
Dextrose	5.31	7.5	22
Cream	3.61	8.5	42
	4.38	9.0	41
	3.98	16.0	42
Cottonseed oil	3.33	16.0	43
Casein	3.81	16.0	37

\* The method of obtaining the values is given in the text.

*Total Acidity of the Gastric Content.*—The total acidity was practically the same with oral as with jejunal feeding when three feedings a day were given, but with five feedings a day the value was higher with jejunal feeding than with oral feeding.

*Hydrogen Ion Concentration of the Duodenal Content.*—In the two dogs with duodenal fistulas in which duodenal specimens were withdrawn, it was noted that the duodenal  $p_H$  was higher with jejunal feeding than with oral feeding and that the  $p_H$  was slightly lower with five feedings than with three feedings daily.

*Psychic Secretion of Gastric Juice.*—It was thought that the high acidity of the juice obtained with jejunal feeding might perhaps be due to psychic secretion, since these dogs would go for periods of four or five days at a time without food by mouth. In order to decide this point, two of the dogs were given sodium amytal by jejunum. It was found that 18 mg. per kilogram of body weight would make the dogs sleep soundly. With the dogs thus anesthetized, the secretion was just as great and the juice was just as acid as when they were awake.

*Effect of Different Food Substances.*—The feeding by jejunum of each of the food substances, including Ivy's preparation, was followed by some secretion of gastric juice. The effect of the various foods on gastric secretion differed markedly (table).

#### COMMENT

The results obtained from this investigation indicate that most foods when placed in the jejunum will stimulate gastric secretion. In these experiments it was found that during fasting the stomach secreted a few centimeters of thick, white mucus, with a  $p_H$  of about 7, which did not contain any free acid and which contained only a little combined acid. This finding was considered to indicate that the gastric mucosa was not secreting. Stimulation of gastric secretion was considered to have occurred when the specimens began to contain free acid and the  $p_H$  decreased.

All the foods used in jejunal feeding appeared to stimulate gastric secretion, but some foods produced greater gastric acidity than others. Thus, feeding sucrose, peptone, butter, flour and eggs was followed by the production of only a small amount of acidity, while feeding cream, Liebig's meat extract, cottonseed oil, casein and glycine was followed by the production of relatively high acidity.

#### SUMMARY

In this study an attempt was made to determine the effect of jejunal feeding on gastric acidity and secretion. Dogs with gastric and jejunal fistulas were used. It was found that a mixture of milk and syrup when fed by jejunum stimulated gastric secretion and increased the acidity of the gastric content. Greater stimulation occurred when the mixture was fed five times daily than when it was fed three times daily, even though the total number of cubic centimeters of the mixture was the same in each instance. The gastric content was more acid and had a lower  $p_H$  when the mixture was fed by jejunum than when it was fed by mouth. The results were the same whether the specimens were obtained through a gastric (intestinal loop type) fistula, by means of a catheter and syringe or through a stomach tube from a dog with no fistula. Psychic secretion was not a factor in these experiments, as was shown by the results obtained when the dogs were under the influence of sodium amytal. A number of simpler food substances were tested, and were found to stimulate gastric secretion in the following order, from least to most: sucrose, peptone, butter, flour, eggs, dextrose, cream, Liebig's extract, glycine, cottonseed oil and casein. The duodenal content was found to be slightly more alkaline following jejunal feeding than following oral feeding.

# EFFECT OF ENEMAS ON INTESTINAL MOTILITY

HJALMAR E. CARLSON, M.D.

ST. PAUL.

AND

THOMAS G. ORR, M.D.

KANSAS CITY, MO.

Various types of enema are recommended for the relief of post-operative abdominal distention. The beneficial action of these enemas has frequently been attributed to a reflex stimulation of the small intestine, but proof of such action has not been found in the literature. That the rate of expulsion of enemas in a dog with an obstruction is similar to that in a normal dog has been shown by Wangensteen and Goehl.<sup>1</sup>

## EXPERIMENTAL METHODS

Kymographic tracings of the ileum and jejunum of normal dogs were taken before, during and after the administration of various enemas. The tracings of the ileum were taken through ileostomy openings which were made just before the experiment was begun. The tracings of the jejunum were made through recently prepared Thiry-Vella loops.<sup>2</sup>

Enemas of tap water, physiologic solution of sodium chloride, hypertonic solution of sodium chloride, soap-suds and a mixture of magnesium sulphate, oxgall, glycerin and water were given. The effect of distending the colon with air was also studied. From 100 to 400 cc. of liquid were used in each enema.

## RESULTS

Enemas of tap water, soap suds, physiologic solution of sodium chloride and a mixture of magnesium sulphate, oxgall, glycerin and water and injections of air did not show any effect on the motility of the small intestine. The only change from the normal tracings occurred when the enemas were being expelled, at which time strong contractions of the rectus muscles compressed the intestine.

Enemas of hypertonic solution of sodium chloride in concentrations of 2, 10 and 20 per cent and saturated solution (about 36 per cent) regularly increased peristalsis in from five to ten minutes. The strong solutions produced the greatest effect. The action of the hypertonic solution of sodium chloride may have been due to the

---

From the University of Kansas School of Medicine.

1. Wangensteen, O. W., and Goehl, R. O.: Evaluation of the Expulsion of Enemas as a Criterion of Intestinal Obstruction, *Arch. Int. Med.* **46**:669 (Oct.) 1930.

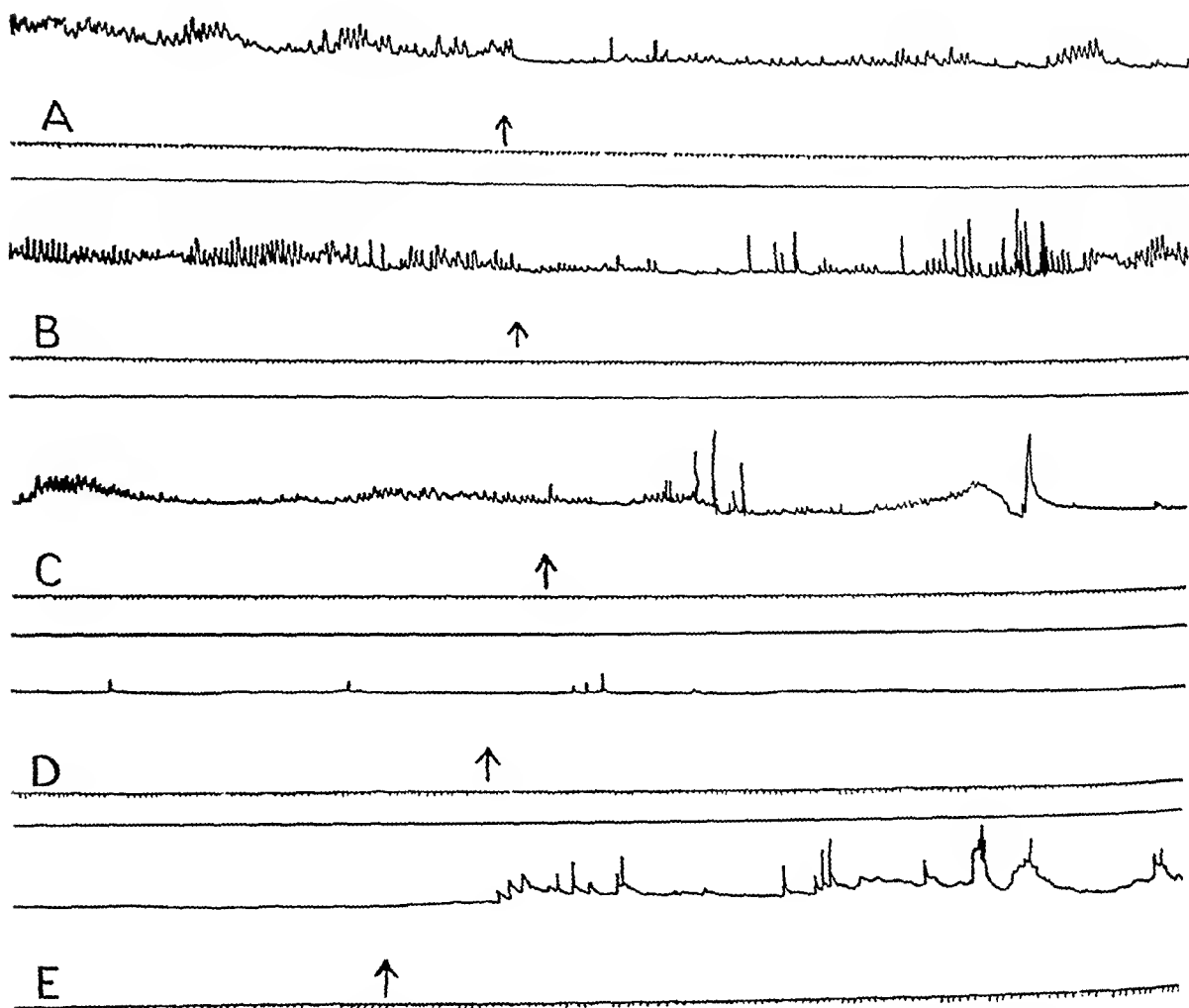
2. Orr, T. G.: The Action of Sodium Chloride upon the Small Intestine, *Ann. Surg.* **94**:732, 1931.



absorption of salt into the blood stream from the colon, since a study of the blood showed an increase in the chloride content in from one to three hours after the injection. The stronger solutions of salt produced severe proctitis.

#### SUMMARY

The action of simple and irritant enemas on the motility of the ileum and jejunum were studied experimentally by recording the con-



Tracings of the ileum and jejunum before and after the injection of various types of enema. In each instance the portion of the tracing to the left of the arrow is of the normal intestine before the injection and the portion to the right is of the intestine after the injection of the specified enema. *A* shows the effect on the ileum of the injection of an enema of 200 cc. of air by rectum; *B*, the effect on the ileum of an enema of 200 cc. of tap water; *C*, the effect on the ileum of an enema of 200 cc. of magnesium sulphate, glycerin, oxgall and water; *D*, the effect on the jejunum of an enema of 400 cc. of soap-suds, and *E*, the effect on the jejunum of an enema of 200 cc. of a 10 per cent solution of sodium chloride. The sharp contractions noted in the first three tracings were caused by the muscular effort to expel the enema. The enema of hypertonic solution of sodium chloride caused an increase in intestinal tone and peristalsis.

tractions of the intestine by means of a rubber balloon before, during and after the enemas were given.

No increase of motility of either the jejunum or the ileum was noted except with hypertonic solutions of sodium chloride. Clinical experiments have not been made with enemas of hypertonic solutions of sodium chloride.

The suggestion that the enemas commonly used are active in relieving abdominal distention by reflex action on the small intestine was not supported by this study. Enemas as usually given should be depended on only to aid in emptying the colon.

# A REVIEW OF UROLOGIC SURGERY

ALBERT J. SCHOLL, M.D.

LOS ANGELES

E. STARR JUDD, M.D.

ROCHESTER, MINN.

JEAN VERBRUGGE, M.D.

ANTWERP, BELGIUM

ALEXANDER B. HEPLER, M.D.

SEATTLE

ROBERT GUTIERREZ, M.D.

NEW YORK

AND

VINCENT J. O'CONOR, M.D.

CHICAGO

## KIDNEY

*Hydronephrosis*.—Lichtenberg<sup>1</sup> described a pathologicophysilogic principle which aids in differentiating the dynamic and the mechanical form of renal obstruction and in selecting the method of surgical treatment with more assurance and success. Testing the response of the pelvic and ureteral musculature to electrical stimulation at the time of operation will reveal whether conservative surgical therapy is indicated. Lichtenberg stated that a pathologicophysilogic point of view of renal obstruction might open up new methods in treatment in those cases in which surgical intervention is not necessary.

Pelliccia<sup>2</sup> discussed the etiology of intermittent hydronephrosis in 2 cases in which he recently had occasion to operate. Defining intermittent hydronephrosis as the phenomenon of successive attacks of acute and sudden retention of urine in the renal pelvis, which are followed within a few hours or during the course of a day by its complete outflow, with no disturbances between attacks, he maintained that the symptoms in such cases are distinctly different from those of common hydronephrosis, as are also the etiologic factors. The particular variations of diuresis are characteristic; urine is scanty during the attack and abundant at its end, and although hematuria is sometimes present the urine is otherwise normal.

---

1. Lichtenberg, A.V.: Die pathologische Physiologie der renalen Verstopfung, und die sich daraus ergebenden konservativ-chirurgischen Massnahmen, Acta chir. Scandinav. **74**:283, 1934.

2. Pelliccia, Gilberto: Due case di idronefrosi intermittenti, Arch. ital. di urol. **11**:246 (April) 1934.

The same causes that produce hydronephrosis in general may give rise to intermittent hydronephrosis, but some of these causes are observed with greater frequency in cases of the latter condition, and it is with these that the author is concerned. Chief among them are malformations, and these may be either congenital or acquired. Among the former are anomalies of the renal pelvis, stenosis of the ureter, valvular folds, anomalous blood vessels and lesions of the nerves. Among acquired malformations are renal ptosis, strictures of the ureter and renal lithiasis.

In the author's first case the patient was a woman 24 years of age, and the intermittent attacks of hydronephrosis dated from the age of 7 years, when they had been mistaken for appendical colic. This led to fruitless appendectomy when the patient was 13 years of age. A sound introduced into the ureter by Pelliccia revealed an S-shaped structure, demonstrating that the ureter deviated greatly from its normal position, possibly because of the descent of the hydronephrotic sac, which reached almost down to the iliac crest. On the basis of the roentgenographic and pathologico-anatomic observations, which revealed that the ureter deviated laterally to a considerable extent on leaving the renal pelvis and that at the start it was markedly contracted. Pelliccia accepts the hypothesis that this stenosis and deviation constituted a congenital malformation which represented the first obstacle to the urinary outflow and that in the factors bringing about polyuria, which may be the result of any one of several causes—stenosis of the ureter or bagpipe shape of the renal pelvis—there was stasis with consequent increase of intrapyloric pressure. This may result in a false valve on the ureteral ostium or may provoke a spasm of the ureter until hypertension reaches a point capable of arresting the secretion of urine and of causing paresis of the ureter, with relaxation of its walls, overcoming the spasmodic closure and permitting the outflow of the urine.

In the second case the sound introduced into the ureter met an obstruction at a point 10 cm. from its orifice into the bladder, beyond which it was markedly contracted. That this stenosis was of congenital origin is confirmed by the abnormality of the vesical orifice. It is logical to assume that the incapacity of the abnormally contracted ureter for permitting the outflow of the increased volume of urine under conditions of increased diuresis to which the patient was subject resulted in stagnation, with distention of the sac. It may be that at such times reflex spasms of the ureter also occurred, which would explain the complete arrest of the outflow sometimes observed. When the increased pressure in the pelvis of the kidney was sufficient to arrest diuresis and the spasm of the ureter was relaxed, spontaneous outflow of the collection occurred.

*Calculi.*—Nash<sup>3</sup> stated that most cases of calculous pyonephrosis occur among young women who marry at an early age and rapidly go through multiple pregnancies. There may be urinary diathesis which predisposes such women to infection and to the formation of a stone in the kidneys, a condition analogous to that of women with biliary diathesis in whom the disease of the gallbladder has its origin at the time of the first pregnancy. The treatment of the acute and of the chronic type was considered. For the latter it was suggested that nephrotomy be done first, to be followed by secondary transperitoneal nephrectomy, because the abdominal approach enables one to avoid hemorrhage and other complications incident to lumbar nephrectomy.

Twinem<sup>4</sup> reported that bilateral involvement is present in about 13 per cent of cases of renal stone. Bilateral lithiasis is usually preceded by a bilateral infection. A bilateral operation should be done only in cases in which the stones can be removed easily, in which the patient is young and in which only slight or no infection is present. Usually the better kidney should be operated on first. Certain exceptions were mentioned. The surgical indications in cases of various types of bilateral stones were discussed. The patient requires the most meticulous care if the best results are to be obtained.

*Tumor.*—Ceccarelli<sup>5</sup> reported a case of an unusual variety of renal adenoma of complex structure, which is not easy to interpret or to classify and a study of which raises important questions with reference to the histogenesis of an entire series of renal tumors of similar structure, variously classified now as hypernephroid tumors and angio-epitheliomas.

At operation on a woman who had suffered from renal colic on the left side a spheroid tumor the size of a mandarin orange was found; the growth was half embedded in the parenchyma and reached the renal pelvis. It was wine red and of a soft and almost fluctuating consistency and was surrounded by a smooth fibrous capsule. From this capsule a great number of trabeculae could be seen entering the interior of the tumor, dividing it into many compartments; coursing through the trabeculae were numerous small blood vessels or dilated capillaries which frequently constituted the entire skeleton of the septum. In some instances epithelial cells rest directly on these. The tumor was thus seen to be an adenomatous new growth in which the vascular

---

3. Nash, I. E.: *Calculous Pyonephrosis: Clinical Study with Especial Reference to Etiology and Treatment; Review of Its Literature; Report of 6 Cases*, *Am. J. Surg.* **24**:110 (April) 1934.

4. Twinem, F. P.: *Surgical Management of Bilateral Nephrolithiasis*, *Am. J. Surg.* **24**:124 (April) 1934.

5. Ceccarelli, G.: *Su di una forma rara di adenoma renale*, *Arch. ital. di urol.* **11**:223 (April) 1934.

element was so strongly developed that it had to be considered an integral part of the tumor. This led the author to inquire whether it might not be possible to classify it among certain varieties of hypernephroid tumors, in which the characteristic vascular development is particularly accentuated and in which there is an intimate relation between blood vessels and epithelial elements.

It is rather worthy of remark that despite this abundance of vessels there had been no macroscopic hematuria, although microscopic hematuria had occurred shortly before operation. The compartments were in some places filled with well conserved blood and in other places chiefly, or almost exclusively, with an amorphous homogeneous substance resembling colloid. Many of the cavities were lined with cylindric or cuboid epithelium or even by flattened elements of endothelial type, and in the lumens of some of the cavities papillary formations were seen protruding.

Ceccarelli, after reviewing the literature, in which considerable controversy is found with reference to the interpretation of similar new growths, concluded that his tumor must be regarded as a papilliferous adenoma, characterized by an unusually abundant vascular development and arising from embryonal rests that consist of epithelial cells and blood vessels of the kidney, which had remained shut off or deviated from the normal. In his opinion it is possible to interpret in this way a considerable number of new growths in the kidney, which are called by different names and are classified sometimes as hypernephroid tumors and sometimes as angio-epitheliomas; all, however, are characterized by the phenomena of blood vessels and epithelial cells growing together in intimate association. A bibliography of twelve references accompanies the article.

MacKenzie<sup>6</sup> stated that it is estimated that on an average the pelvic tumors comprise about from 5 to 7 per cent of all renal growths. Papillary growths represent about from 70 to 80 per cent of all tumors of the renal pelvis. Of these, from 60 to 70 per cent are benign and from 30 to 40 per cent are malignant. Several of them are on the borderline. The papillary growths of the renal pelvis are similar to the papillary growths of the bladder. They appear alike, they have the same characteristic property of forming transplants, and they simulate each other in their low grade malignancy. The simple papillomas are usually multiple and appear as villous or wartlike growths. Occasionally the growth has an extensive distribution and may involve the ureter and the bladder and even the ureter on the opposite side. Often there is one large growth with several smaller

6. MacKenzie, D. W.: Papillary Growths of the Renal Pelvis, *Canad. M. A. J.* 30:509 (May) 1934.

ones surrounding it. Frequently the growths are associated with salty incrustations and even with definite calculi. The papillomas are all very vascular and bleed easily. This accounts for the marked hematuria that is usually the outstanding symptom in the disease. The growths are benign, but have a tendency, like the simple papillomas of the bladder, to become malignant. They do not metastasize but possess the quality of producing transplants along the ureter and in the bladder. The malignant papillomas are also wartlike or cauliflower-like in character but appear more compact and usually involve a greater area than the simple papillomas. At times the entire kidney is replaced by a growth. The villous processes are not as long or branching and often show areas of ulceration. Here, too, the growth may extend downward to involve the ureter and the bladder. In the early stages there is definite evidence of involvement of the submucosa, and later the renal parenchyma is encroached on. In most advanced cases there is distention of the renal pelvis and multiple cysts are present in the cortex of the kidneys. These tumors are also extremely vascular and bleed easily. Microscopically the essential tumor cells are found to have invaded the base of the growth and the submucosa. In some growths there are areas showing benign and malignant cells side by side, suggesting a transformation from a benign to a malignant state.

*Carcinoma.*—Gilbert and MacMillan<sup>7</sup> stated that primary squamous cell tumors of the renal pelvis are relatively rare, as approximately 57 cases have been previously reported. Thirty-one were in males and 26 were in females. The tumor occurred 26 times on the left side and 26 times on the right side, while in 5 cases the side involved was not stated. Pyuria was noted 39 times. This was consistently present in the cases coexisting with calculi and leukoplakia. This combination of infection and calculi led to the diagnosis of calculous pyonephrosis in most cases. Thirty of the 57 cases, or 52 per cent of squamous cell tumors of the pelvis of the kidney, were associated with calculi. These reports showed that calculi varied greatly in number, size and chemical structure. Multiple calculi were not unusual, and the calculi were frequently large. The growth in 31 cases was classified as squamous cell carcinoma, in 11 as epithelioma, in 9 as pavement cell epithelioma, in 3 as epidermoid carcinoma and in 1 case as scirrhous carcinoma, epithelioma carcinoid and "flat carcinomatous ulcer." Twenty-four cases, or 42 per cent of this series, were observed at necropsy. In other cases exploratory operation proved the presence of metastasis. Clinical examination alone often revealed the presence of widespread disease, as in Hartmann's case. Direct extension from the renal artery to the

---

7. Gilbert, J. B., and MacMillan, S. F.: Cancer of the Kidney, *Ann. Surg.* 100:429 (Sept.) 1934.

vena cava occurred 5 times, and to the local lymph nodes, 9 times. Metastasis to bones was noted 8 times; the adjacent vertebrae were involved 5 times, and the seventh rib, the greater trochanter of the femur and the lower end of the femur were each involved once. Only early surgical removal of the carcinoma can save these patients. It is generally agreed that the diagnosis is made late in the course of the disease, when the kidney is fixed or when metastasis has already taken place. In several instances, nephrectomy for stone was carried out and the presence of tumor was not suspected. In other cases nephrectomy was done for drainage when the tumor was inoperable. In 18 cases no operative procedure was done. Operative procedures were carried out as follows: exploratory operation, 7 times; nephrotomy, 6 times, and nephrectomy, 36 times. In 15 cases of this series the length of life and the cause of death were not stated. Eight patients are reported to have died; 6 patients are reported to have had recurrence after operation, which caused death in between six months and one year; 26 patients died in the first six months after operation. Gilbert and Mac-Millan said that there were no five year cures in this series. The fact that these tumors are generally of a high degree of malignancy and that the clinical diagnosis is made late combine to make this disease uniformly fatal.

Keen<sup>8</sup> called attention to the similarity of the roentgenographic appearance of malignant and that of tuberculous (renal) calcification. Thirteen cases of unilateral renal malignant disease and associated tuberculosis were reviewed. A case of renal tuberculosis on the right side and hypernephroma on the left was presented. Evidence was offered toward the supposition that the original lesion in the left kidney was of tuberculous origin. Ten of these cases have been reported since 1925. This indicates that one must consider the coexistence of these lesions in the urinary system with more than passing interest.

*Horseshoe Kidney.*—Sorrentino<sup>9</sup> had occasion to operate on 2 horseshoe kidneys, 1 of them affected with hydronephrosis and the other with tuberculosis. In the first case the pyelogram revealed the characteristic inward rotation of the calices, with marked dilatation of those on the left side. The image of the ureters began at the lowermost part of the shadow of the renal pelves, and both ureters, shorter than normal, followed a course converging from above downward and from without inward. The bilateral pyelogram led to a preoperative diagnosis of hydronephrosis in one half of a horseshoe kidney on the left side, for which the author performed nephrectomy by the lumbar route.

8. Keen, M. R.: Associated Renal Tuberculosis and Malignancy, *Am. J. Surg.* 25:467 (Sept.) 1934.

9. Sorrentino, Michelangelo: Contributo alla chirurgia del rene a ferro di cavallo, *Arch. ital. di urol.* 11:262 (April) 1934.



In the second case no pyelogram was made, owing to the patient's refusal to permit it, but the indications for removal of the right kidney were so clear that the author removed it; it was discovered at operation to be a horseshoe kidney in which the isthmus was composed of parenchymal tissue. In both cases uneventful recovery followed operation.

Sorrentino expressed the opinion that the majority of fused kidneys produce no symptoms and are discovered only by accident at necropsy. In his two cases neither patient had the slightest trouble from the malformation until urinary disturbances began, in one case four years, and in the other one year, before observation.

The most efficient aid in diagnosis is the pyelographic image, which reveals the sagging of the renal pelves, their approach to the median line, the indistinct image of the isthmus, the enormous obliquity of the two renal masses from above downward and from without inward and also the divergence of the ureters from below upward, which results anatomically from the rotation of the renal hilus. This sign is not always clearly revealed, but when it is present it has great value.

The deformation of pelves and ureters is seen particularly well in sagittal projection, which causes the shadow of the pelvis to appear elongated, with variations of caliber at different levels and with the calices oriented to the right or to the left or upward in the form of rounded stumps; they are nearly always dilated and abnormally swollen. The pyelogram shows how the ureter starts from the lowermost and most median point of the shadow of the renal pelvis.

As regards treatment, nephrectomy is the method of choice. Sorrentino insisted on the impropriety of calling such a procedure a heminephrectomy, since the removal of one side of the horseshoe mass is in reality a true nephrectomy, the only difference from the usual nephrectomy being the greater difficulty of exteriorization because of the fixity of the organ and the greater operative dangers owing to its greater vascularity and the presence of the isthmus. The transperitoneal approach is to be condemned and should never be used in cases diagnosed before operation.

In performing symphysiotomy it is important to expose the isthmus completely, and for this its accurate isolation is necessary. Sorrentino advised that the isthmus be sectioned not too far from the kidney to be removed, since this enables the surgeon to use a zone supplied mainly by vessels that have been already tied, thus decreasing the amount of hemorrhage. If the isthmus is thin and fibrous, it should be sectioned vertically and sutured with a stitch or two; but if it is parenchymatous and from 2 to 4 cm. thick, a more precise technic is necessary, extreme care being employed to provide for complete hemo-

tasis before an incision is made; Sorrentino employs a flap which he fixes with two U-shaped sutures. In this way he avoids all hemorrhage.

[COMPILER'S NOTE.—The early clinical manifestations of disease of a horseshoe kidney can usually be recognized when a good clinical history has been taken and a careful physical examination has been made. It is almost universal to find that these patients have gone for years with symptoms that are not properly recognized until a concomitant infection brings the patients to the urologist for examination.

The removal of half of the horseshoe kidney for associated pathologic changes should properly be called heminephrectomy since the two kidneys have become a single organ. It appears that in disease of a horseshoe kidney the best procedure is division of the isthmus, or symphysiotomy, when the isthmus is small and fibrous, but when it is large and composed of true renal parenchyma an operation combining symphysiectomy, nephrolysis, ureterolysis and nephropexy is the one of choice.

Sorrentino has properly called attention to the disadvantages of the transperitoneal approach when the organ can be reached by the extra-peritoneal route, in order to avoid peritoneal infection.]

*Thrombosis of the Renal Veins.*—Hepler<sup>10</sup> reviewed the literature on thrombosis of the renal veins and studied the 40 cases presented therein, in addition to reporting 2 personally observed cases.

Although 30 of the 40 cases studied were reported as clinical observations and in 22 there were definite symptoms referable to the kidney, and although the syndrome of thrombosis of the renal veins is clearcut, in no instance has a diagnosis ever been made with pathologic confirmation, either by operation or by necropsy.

The subject becomes of some clinical importance because of the possibility of relief by surgical measures when one considers that in half of the cases the thrombosis was unilateral and that in many instances the hemorrhagic infarction was the predominant clinical lesion, despite the fact that in other cases the primary disease overshadowed it. Undoubtedly recovery from the associated disease is prevented by the onset of the infarction, and its early recognition and treatment would modify the outcome in a number of cases.

A classification of thrombosis of the renal veins is submitted; this is based on the origin of the thrombi and the conditions attending their growth. In regard to the presence or absence of infection in the thrombi, the terms suppurative and nonsuppurative are suggested in place of the ones commonly used, septic and aseptic. Practically all thrombi start on the basis of infection and are associated with some

10. Hepler, A. B.: Thrombosis of the Renal Veins, *J. Urol.* **31**:527 (April) 1934.

degree of thrombophlebitis or bacterial injury to the intima, either in the capillaries or in the veins. There may be no active infection or suppuration in the secondary extension to the renal veins, but at its source the thrombus arises from phlebitis. Therefore, it seems better to designate the so-called aseptic thrombi as nonsuppurative and the definitely infected thrombi as suppurative. A complete analysis is made of the pathologic and clinical features of the cases reported.

Hepler's first case was one of postscarlatinal thrombosis of the vena cava which evidently existed for some time with the establishment of a collateral collection. Visceral involvement was late and started as a hemorrhagic infarction of the left kidney from a secondary thrombus in the left renal vein.

Recovery after removal of the left kidney was prevented by secondary thrombosis of the right renal vein ten days later. However, the marked improvement following nephrectomy indicates the feasibility of surgical intervention, even in the presence of extensive extrarenal thromboses, if the condition is unilateral, as it is in half of the cases reported, and if the infarction is not overshadowed by the primary or associated disease. The fact that this lesion presents a definite clear-cut syndrome consisting of sudden onset of hematuria, pain and tenderness in the lumbar region and rapid progressive enlargement of the kidney should insure its more frequent clinical recognition. With this presumptive evidence, the additional cystoscopic findings of unilateral bleeding, reduction or absence of function and enlargement of the outline of the kidney with no shadows on excretory urography are diagnostic.

The condition is not uncommon in infants; in them it is usually primary and associated with severe enteritis which overshadows the infarction and precludes the possibility of surgical intervention. At the time of total infarction of one kidney there is frequently beginning capillary thrombosis on the opposite side. However, in older children and adults the thrombosis is usually secondary and unilateral.

Although practically all thrombi arise on the basis of infection, suppurative thrombophlebitis is rare among infants. It usually occurs between the ages of 25 and 50 years and is secondary to severe suppurative lesions of the kidney, either hematogenous or ascending. In the surgical treatment of pyogenic infections of the kidneys the possibility of an infected thrombus in the renal veins as a continued source of blood stream infection must be considered.

*Decapsulation.*—Lioy,<sup>11</sup> who is an advocate of decapsulation in cases of nephritis, made a clinico-operative study of certain types of

---

11. Lioy, D.: Considerazioni clinico-operative su alcuni casi di nefrite acuta e dolorosa, Arch. ital. di urol. 11:115 (Feb.) 1934.

nephritis in which the chief symptom was pain or hematuria or both of these combined. He observed that pain and hematuria do not in all cases go *pari passu*, but that in some cases one, and in others the other, of these symptoms predominates, while in a certain number the two are so intimately connected as to be inseparable. As a rule, in the class of cases discussed the lesions are unilateral; in the 8 cases which serve as an illustrative basis for this work there was only 1 in which the second kidney became involved about a month after the involvement of the first kidney.

In all cases operation (decapsulation) has revealed pathologico-anatomic changes in the kidney (enlargement, congestion, fibrous reaction, etc.) and its capsular coverings. The capsule proper was found in every case to be thickened and closely adherent to the organ, so that in some cases extreme caution had to be exercised in its removal to avoid injuring the renal substance and provoking secondary hemorrhages, which are dangerous for the postoperative course. The fatty capsule, too, has been found to be more or less the victim of the pathologic changes of sclero-adiposis. The fibrous connective tissue trabeculae were sometimes in such close connection with the capsule proper as to form a network of plastic adhesions which had to be removed *en bloc* with the fibrous capsule.

After decapsulation, a systematic search for calculi was made by manual and instrumental palpation. The size of the kidney was always larger than normal, and this was also confirmed by preliminary roentgenograms.

Conservative surgical treatment, that is, decapsulation, brought complete cure in all cases, with permanent good results and disappearance of every disturbance. This operation has proved effective, even in cases in which the morbid process dated back for a year or so. Hence, it seems probable that decapsulation favors the intrarenal circulatory apparatus, and that sclerofibrous changes have not the slightest importance for the perinephrium, whether they are primary or secondary, in the process of chronic nephritis.

The author concludes that nephrotomy for exploratory purposes in doubtful cases of calculosis, of which there were 2, did no injury, either mediate or immediate, with respect to operative results beyond prolonging to a negligible extent the time required for operation. All the good results have been maintained from the one to six years that the cases have been under observation, up to the present time. Pyelography was done in only one or two cases in which general and local conditions permitted. In 2 cases the author found that an iopax derivative (known abroad as uroselectan B) administered intravenously had a remarkable hemostatic action in nephrorrhagia and arrested hemorrhage instantly.

A long and comprehensive bibliography accompanies this article.

[COMPILER'S NOTE.—Renal decapsulation has received preponderant study in the literature, particularly since the work of Edebohls, who reported more than 100 cases of bilateral renal decapsulation for Bright's disease. This work, however, has not withstood the test of time, although the procedure has its indications and good results have been obtained in some cases. It has been proved by necropsy in some cases in which the patients had been subjected to this operation that the capsule proper of the kidney will regenerate within a certain period of time, and therefore the procedure seldom has a permanent curative result.]

*Nephropexy.*—Stroke<sup>12</sup> described the operation of suspension of the kidney by the use of fascia lata. The kidney was exposed by an oblique incision. It was freed of all perirenal tissue down to the capsule and drawn up to its normal position. A strip of fascia lata, from 8 to 10 inches (20 to 25 cm.) in length and  $\frac{3}{4}$  inch (1.9 cm.) in breadth, was then obtained from the leg. After it was cleansed of all adherent fat, the strip of the fascia was passed around the lower pole of the kidney, beneath the capsule. It has seemed unnecessary to suture the kidney or the capsule to the fascial strip. Chromic catgut was used in suturing the overlapped fascia. The incision was closed in the usual manner. No attempt was made to close the defect left in the fascia lata, as previous experience has shown this to be unnecessary. Careful hemostasis is imperative to prevent subsequent hematoma, and as an additional safeguard a rubber tissue drain through a stab wound below the line of closure is advisable. Stroke stated that while neither a sufficient number of cases nor the test of time has made the operation as described one of proved merit, the underlying principles have been so well proved as to make the element of error negligible.

*Renal Function.*—Walters and Counseller<sup>13</sup> stated that the ability of the body to develop an adequate renal reserve is shown by the remarkable hypertrophy which takes place in a solitary kidney or in a remaining kidney following nephrectomy. In the presence of stones in the kidney or ureter and incomplete obstruction producing hydro-nephrosis the various tests of renal function do not give accurate indexes of the function of the kidney. Much valuable renal tissue may therefore survive long periods of partial or incomplete obstruction. This difference between the actual ability of a kidney to function and that indicated when tests are made may be accounted for by the fact that excretion, on test, is interfered with by the resting state of

---

12. Stroke, J. E.: Kidney Suspension by Use of Fascia Lata, *J. Urol.* **32**:171 (Aug.) 1934.

13. Walters, Waltman, and Counseller, V. S.: The Restoration of Renal Function, *J. Urol.* **31**:649 (May) 1934.

glomerular activity noted by Richards, by pyelovenous backflow and by the uncertain reflex action of a stone in the kidney or the ureter.

The return of the excretory renal function following removal of stones in the ureter and kidney in cases of unilateral or bilateral renal injury, as well as the rapid return to normal of a dilated ureter and renal pelvis after removal of an obstruction, is remarkable. The rapidity with which function of the kidney returns depends on the presence of sufficient renal parenchymal tissue which is anatomically and physiologically sound, provided complete relief of the obstruction and adequate control of the infection can be obtained.

It is advisable to remove stones in the ureter or kidney or to remove other obstructing lesions before extensive destruction of the renal parenchyma takes place, especially when a solitary kidney is present. When there is no appreciable return of renal function, as evidenced by increasing excretion of phenolsulphonphthalein and reduction in the value for blood urea, and urinary obstruction has been completely relieved, one has presumptive evidence that serious injury to the kidney has occurred.

Herbst and Baumrucker<sup>14</sup> described a new colorimetric test for renal function using intravenous injection of diodrast.

The test is performed as follows: a specimen of urine containing excreted neoskiodan is diluted to 1000 c.c. One half cubic centimeter is placed in a pyrex test tube and evaporated to dryness; three drops of a saturated solution of potassium nitrate are added, and again evaporated to dryness; 2 cc. of concentrated sulphuric acid are added, and the whole is cooked and heated. It is then cooled, water added, cooled again. It is then shaken with 2 c.c. of chloroform and compared to a colorimeter. The entire procedure is performed in the same test tube from evaporation to color comparison and does not take more than seven to ten minutes.

The color scale may be made by dissolving 100 mg. of iodine in 128.5 c.c. of chloroform and adding 0.1 c.c. of this solution for each 5 per cent, diluting up to 2 c.c. with chloroform.

The acidified iodine chloroform solution has a slightly deeper shade than the plain iodine chloroform solution. This can be corrected by layering a few cubic centimeters of water, acidified with sulphuric acid, over the iodine-chloroform solution. . . . This test, unlike the phthalein test, can be performed on bloody urine. The urine is diluted to 1000 c.c. to have it correspond more closely to the phthalein test. However, in children where only one-half of an ampoule is used, it may be diluted to 500 c.c. instead and performed as described.

*Pyelonephritis.*—Rose<sup>15</sup> stated that in cases of postpartum pyelonephrosis with retention of urine in which catheterization is indicated

14. Herbst, R. H., and Baumrucker, G. O.: A New Colorimetric Test for Renal Function Using Intravenous Iodine Preparations: A Preliminary Report, *J. Urol.* 32:131 (Aug.) 1934.

15. Rose, D. K.: Postpartum Pyelitis of Pregnancy: Treatment of Certain Cases Without Use of Ureteral Catheter; Explanation Based on Physiology of Bladder, *Am. J. Surg.* 25:394 (Sept.) 1934.

on account of either dysuria or toxicity he met with two entirely opposite types of function of the bladder. Either may exist separately, or the two may coexist to any degree. The bladder showing a relatively fixed, compensated wall back of a physiologic block, motor and sensory, of the external sphincter following parturition, if of sufficient degree, requires continuous drainage when indicated by reason of infection. Such drainage reduces, primarily, infection of the bladder and, secondarily, the urethral, pelvic and renal infection by facilitating urinary flow through a decompressed and perfectly drained bladder. Intermittent catheterization in such a bladder traumatizes in the presence of imperfect drainage and, therefore, tends to generalize or to diffuse the infection. The instillation of irritative preparations into such a bladder is contraindicated. If a sufficient degree of altered function of the organ occurs, continuous drainage is indicated until perfect function is restored. The bladder with inhibited or functionally weakened walls and with normal tone of the sphincter following operation requires only intermittent catheterization.

Sisk, Wear and Cummings<sup>16</sup> stated that acute pyelonephritis may cause great destruction of the cortex of the kidney and reduction in function. The inflammation in the wall of the pelvis and ureter and in the peripelvic and periureteral tissues may interfere with drainage early in the course of the disease by diminution in the caliber of the lumen and by lessening of peristalsis. Marked dilatation in the pelvis and ureter may occur without demonstrable evidence of stricture. Great stasis of urine may occur, as evidenced by an emptying time of seventy-five minutes in 1 case which was reported. This increases the intrarenal pressure and increases the tendency of the infection to invade the cortex. Nephrostomy offers a means of giving constant and complete drainage and should be carried out before great renal damage has occurred. Drainage may be temporary or permanent, depending on the progress of the case. In many cases nephrostomy will conserve renal function, and in some cases it will save the patient's life.

*Perinephritic Abscess.*—Shane and Harris,<sup>17</sup> after reviewing the literature and studying the roentgenograms made in 40 cases in which operation was performed for perinephritic abscess at the Mayo Clinic, concluded that the roentgenographic signs of perinephritic abscess must be considered as a valuable adjunct in the diagnosis of this condition. The shadow of the psoas muscle was obliterated to some extent in all cases; some abnormality of the renal shadow was found in 33 cases (80.2 per cent); scoliosis was found in 18 (28.1 per cent) of the 32

---

16. Sisk, I. R.; Wear, J. B., and Cummings, E. F.: Nephrostomy in Pyelonephritis, *Am. J. Surg.* **25**:451 (Sept.) 1934.

17. Shane, J. H., and Harris, Milo: Roentgenologic Diagnosis of Perinephritic Abscess, *J. Urol.* **32**:19 (July) 1934.

cases in which roentgenologic examination of the thorax was made. In 22 cases (55 per cent) an associated pathologic condition was found at operation, stones being present in 17 cases (40.2 per cent). The frequency with which obliteration of the shadow of the psoas muscle occurs on one or both sides and the frequency with which some degree of scoliosis is found in the course of routine roentgenography diminish to some extent the clinical value of these data. For instance, the shadow of the psoas muscle was obliterated on one side in 10 per cent of cases and on both sides in 3 per cent. Definite scoliosis was present in 3 per cent of cases, but there were several other roentgenograms in which it occurred, in the opinion of some observers; according to others, however, it was absent. The roentgenograms were studied in a series of 50 cases of renal calculi, and obliteration of the psoas muscle, or scoliosis, was found to some extent in over 30 per cent of these cases. The roentgenologic signs of perinephritic abscess, especially obliteration of the shadow of the psoas muscle or scoliosis, do not necessarily indicate the existence of perinephritic abscess and therefore cannot be regarded as pathognomonic. They have a relative importance, however, when considered in conjunction with the clinical manifestations of the disease, which is increased when coincident scoliosis and obliteration of the psoas muscle are observed.

*Paranephritic Abscess.*—Brown<sup>18</sup> reported in detail his third case to prove that there exists a type of traumatic abscess of the back which involves the contents of the paranephric space and which is the result of trauma to the muscle accompanied with hemorrhage. The first result of the trauma is interstitial myositis in which, if infection follows, small abscesses form; these may coalesce and, with the infected hematoma, form a large abscess. This type of abscess is distinct from the abscess involving the perirenal fat and might more properly be designated paranephric than perinephritic abscess.

*Tumors.*—Bergendal<sup>19</sup> reported a case of carcinoma of the ureter. He collected the reports of 26 additional cases from the literature and combined these cases with the 49 cases previously analyzed by Roussetot and Lamon and reviewed the entire group, a total of 76 cases. Forty-three of the patients were men and 33 were women. Such a distinct predominance of men was not noted in earlier series. The age of 1 patient was not stated, but the age distribution of the others was as follows: 30 to 39 years, 4 patients; 40 to 49 years, 18; 50 to 59 years, 20; 60 to 69 years, 22; 70 to 79 years, 9, and 80 to 89 years, 2.

18. Brown, Alfred: Traumatic Infected Interstitial Myositis as a Cause of Paranephritic Abscess, J. A. M. A. **102**:2096 (June 23) 1934.

19. Bergendal, Seved: Clinical Study of Malignant Tumors of the Ureter: An Operative Case of Ureteral Sarcoma, Acta chir. Scandinav. **74**:179, 1934.



The youngest patient was 30 years of age and the oldest, 89. According to Bachrach, carcinoma of the ureter occurs at a relatively early age compared with malignant tumors of other organs. In this series 22 of 75 cases (29 per cent) were in persons under 50 years of age. In 41 cases carcinoma was found in the right ureter, and in 35 cases it was in the left ureter. Sufficient information for judging what part of the ureter was the seat of the carcinoma is given in 72 cases, and the distribution is as follows: In 13 cases it was in the upper part; in 10, in the middle part; in 7, at the crossing of the iliac vessels, and in 39, in the lower part; in 2 cases practically the entire ureter was involved, and in 1 case there was a multiple localization in which no definite primary tumor was indicated. A striking feature is the great number of tumors which were found in the lower part of the ureter, where more than one-half were localized. This preference for the lower part of the ureter is well known from previous comparisons. In no fewer than 12 cases the growth either belonged to the ureteral orifice itself or had penetrated the opening so that it could be detected with the cystoscope. Macroscopically the ureteral carcinomas differ widely in appearance. Three types of ureteral carcinoma are most common. The first is the sharply outlined tumor which varies in size from that of a pea or cherry up to that of a pigeon's egg and which fills the lumen and springs from the ureteral wall by a not infrequently narrow pedicle; the surface may be smooth, moderately uneven, split up or papillomatous and cauliflower-like. In the second, or the infiltrative, type the growth invades the ureteral wall for a shorter or longer distance, mostly circularly, constricting the lumen to a greater or lesser degree. If only a short part of the ureter is involved, it may be difficult to determine macroscopically whether a benign stricture or a malignant process is the source of the trouble. On the other hand, cases have been described in which the tumor tissue advances and infiltrates a large portion of the ureter. In the third, or multiple, type the gross appearance may so nearly resemble the picture of multiple papilloma that it is surprising when the malignant nature of the process is discovered at the microscopic examination or manifests itself by metastasizing via the lymph passages. The microscopic structure of carcinoma of the ureter may vary. Histopathologic data were given in 75 of the cases; there were 38 cases of papillary carcinoma, 12 of squamous cell carcinoma, 20 of carcinoma simplex solidum medullare, 3 of adenocarcinoma and 2 of transition cell carcinoma. Exactly half of the cases were of the papillary type. Some of the papillary carcinomas, however, also presented flat epithelial cells. Areas of a distinctly papillary structure were also found often in the tumors in the other groups. Keratinization was observed in at least 2 of the squamous cell carcinomas. The great frequency of papillary carcinoma

has been pointed out by several authors. Carcinomas of the ureter may disseminate in two ways: namely, by implantation and by metastasis by way of the lymphatics. Bergendal stated that there are reports of necropsy in 32 of the cases of ureteral carcinoma; in 22 of these metastasis is mentioned. In at least 1 case metastasis of the lymphatic glands was found at operation. The topographic distribution of metastasis found at necropsy was as follows: in 20 cases it was in the lymph nodes; in 11, in the liver; in 7, in the lungs; in 3, in the osseous system, and in 2, in the pancreas. Among the 76 cases of ureteral carcinoma under review, concretions appear to have occurred in 8 cases, or 11 per cent. Bergendal stated that as in cases of renal tumor the most important symptoms in cases of tumor of the ureter are hematuria, palpable tumor and pain. Of these three symptoms, hematuria, that is, the macroscopic form, may undoubtedly be said to be the most important. Bachrach stated that hematuria occurs in about 45 per cent of all the cases of tumor of the ureter; according to Tiitinen, it is found in about 70 per cent of the cases of carcinoma of the ureter. Bergendal found hematuria mentioned in 54 (75 per cent) of the 72 cases. Pain is also a common symptom of carcinoma of the ureter. Mention is made of pain in 49 of the 72 cases (68 per cent). A study of the literature also shows that particularly during recent years nephro-ureterectomy has been the surgical procedure adopted in most of the cases of malignant tumor of the ureter. This extensive operation has often been performed in one stage. Against this procedure it may be objected that it is a serious operation, especially for debilitated and elderly persons. In the 27 recent cases of carcinoma of the ureter the reports of which have been collected by Bergendal the operation was performed on 10 patients. Of these, no fewer than 4 died after the operation. Bergendal stated that complete nephro-ureterectomy in one stage is regarded as the normal method for the patient whose condition does not directly contraindicate so extensive an operation. Follow-up reports are available only for some of the cases in which operation was performed. Most of the patients died of metastasis or local recurrences a short time after the operation. Only in 6 cases was there a report to the effect that the patient was healthy one year or longer after the operation. At present, therefore, Bergendal feels that the results of the therapy in cases of malignant tumor of the ureter are not encouraging.

*Uretero-Intestinal Anastomosis.*—Higgins<sup>20</sup> presented a new technic for simultaneous bilateral transplantation of the ureters into the rectum, in which the normal course of the urine and continuity of the ureter

20. Higgins, C. C.: Aseptic Uretero-Intestinal Anastomosis, *J. Urol.* **31**:791 (June) 1934.

are preserved until after the formation of a new channel between the ureter and the rectosigmoid. The rectum is exposed and the ureter is dissected out and transplanted without disturbing the bladder. Several days later, at a second operation, the ureter is separated from the bladder, and the lower end is ligated.

The procedure is attended by no interruption of renal function during the establishment of the new channel between the ureter and the intestine. The mortality in experimental animals has been practically negligible. There has been almost complete absence of peritonitis and acute renal infection. The immediate results in 8 clinical cases have been unusually satisfactory, but insufficient time has elapsed to warrant any statement as to the ultimate results.

#### BLADDER

*Tumors.*—Barringer<sup>21</sup> reported the results in 78 controlled cases of carcinoma of the bladder, which were selected mainly from the cases of patients treated by radium at the Memorial Hospital during the past eighteen years. Of the 78 tumors, 48 were graded according to the scheme of Broders. Nine were of grade 1; 24, of grade 2; 14, of grade 3, and 1, of grade 4. In 55 cases the pathologist made an attempt to determine whether the tumor was radiosensitive; 27 tumors were thought to be radioresistant and 28 were considered radiosensitive. Barringer stated that the suprapubic operation with radium implantation is a relatively benign operation. In his first 109 consecutive cases, 4 patients died in the hospital, an operative mortality of 3.6 per cent. In 179 consecutive cases the operative mortality increased; 13 patients died in the hospital, giving an operative mortality of 7.2 per cent. Barringer stated that if it is considered that in the majority of these cases, from the surgeon's standpoint, the condition was inoperable (if one excludes total cystectomy), it will be realized that this is a low mortality. In 7 cases he performed a second cystotomy and radium implantation, while in another case he opened the bladder three times in a vain attempt to control the growth. In 1 of these 8 cases death occurred in the hospital after operation. The great majority of patients were between the ages of 50 and 60 (33 patients) and 60 and 70 years (25 patients); 1 patient was between 30 and 40 years and 4 were between 70 and 80 years. A patient was not considered well unless he had been without symptoms for a sufficient length of time, a year or more, or unless the bladder had proved to be free from tumor by cystoscopic examination or as seen through a cystotomy wound (this operation being done for some complicating process). Thirty-one patients were well after from

---

21. Barringer, B. S.: Carcinoma of the Bladder, Surg., Gynec. & Obst. 58: 867 (May) 1934.

five to ten years; 10 patients, after from ten to fifteen years, and 1 patient after from fifteen to twenty years. Barringer stated that the size of the tumor has no relation to the curability; the size and the position of the base have a direct relation to whether the growth can be controlled. A tumor may fill the bladder and yet may be pedunculated and attached to the wall of the bladder by a very small base. Such tumors are, of course, favorable for treatment by radium implantation. It is interesting to note that in 74 cases in which the size of the base was given, all but 37 of the tumors had a base larger than 6 sq. cm.; 4 were recorded as extensive, and 7 had a base larger than 30 sq. cm. Barringer has classified the tumors as to site into 4 divisions. The first group included tumors of the base of the bladder, touching the trigon, ureters or internal urethral orifice. There were 48 such tumors, a large majority. Of the others, 15 were on the lateral walls, 8 were on the base back of the trigon, and but 2 involved the vault of the bladder. In 5 cases the site was not given. The fact that in a large majority of cases the tumor was situated on, or adjacent to, the trigon makes the operation so signally difficult.

*Exstrophy.*—Marion<sup>22</sup> stated that he has had occasion in no less than a dozen cases to close a ruptured bladder in a female and to reconstruct the urethra by a simple procedure, the results of which have stood the test of time. In his earlier cases this procedure consisted of taking a tubular graft of mucosa from the vagina and placing it in a tunnel excavated between the bladder and the exterior surface of the body. This was done by means of a trocar, through which was passed the vaginal mucosa which was wrapped around a catheter. More recently he has found that as good results can be obtained by a simple tunneling and insertion of a catheter, without the use of a graft, the only difference being that a little longer time was necessary for epidermization of the tract thus formed. Such constructed urethras require continuous supervision over a long period of time. The patients are taught the use of bougies, which at first are passed daily and later at intervals not to exceed three or four weeks, a little dilation occasionally being necessary. The new urethras are permeable, and they also prove to be absolutely continent, the continence being pathologic, resulting from the enclosure of the new canal in tissues which are more or less fibrous. The method is invaluable for use in cases in which the urethra has been completely destroyed during parturition. Recently, Marion used the method in a case of exstrophy of the bladder, cure resulting. If the early results are maintained, this condition will cease to be the redoubtable malformation which it has been considered. The operation should

22. Marion, G.: De la constitution d'un urètre continent chez la femme et de son emploi dans l'exstrophie vesicale, *J. d'urol.* 37:393 (May) 1934.

not, however, be attempted on a child less than 10 years of age. A flap taken from the achilles tendon is wrapped, with its raw surface outward, about a no. 18 Pezzer catheter and is drawn through an excavation which has been made with a trocar between the vagina and the bladder; if the child is a girl, this commences immediately above the vaginal opening and terminates at the bottom of the bladder, behind the interureteral line; the flap then assumes automatically the correct position. The margins of the bladder are now freed by an incision, which passes all the way around the organ; the latter is separated from the deep parts, and the muscular wall is removed over a tract from 2 to 3 cm. long. This gives rise to considerable bleeding, which must be controlled by clamps and tampons. When the bladder has been freed, care must be taken to unroll its edges, which have been rolled up. This is done by sectioning the tissues on the external surface of the bladder to from 1 to 2 cm. from its edges, to make the walls of the bladder susceptible of ready coaptation. The edges of the bladder are sutured transversely or vertically, whichever is easier, reserving an orifice for the placing of a second catheter to deviate the urine. The sheath of the large rectus muscle is then incised longitudinally as far as possible, and the aponeurosis, which forms the anterior wall of the sheath, is separated in such a way that it can be turned back toward the median line and sutured to the opposite side except at the point where the Pezzer catheter is placed. The skin around the bladder is sutured by means of a silver wire and is drawn toward the median line. In some cases flaps may be necessary to secure a complete covering. These may be obtained by undercutting about 3 cm. from the edges of the skin on each side, the two extremities of both flaps remaining adherent to the tissue beneath, while the flaps themselves are drawn together to meet in the median line; the gaps left by the undercutting close later by second intention. The Pezzer catheters must be kept in place as long as possible and must remain patent; this is accomplished not by injections into the catheters but by the use of bougies. They should be changed only when they cease to be patent; if possible, the lower one should not be disturbed for two weeks in order to allow the graft to adhere. After the urethral tract is well established and can be easily catheterized, the upper fistula is closed. In male children the new urethra will go from the bladder to the perineum; the dissection of the lower part of the bladder will pass above the verumontanum and separate the urinary part completely from the genital part. When repair of the exstrophy has been obtained, the upper canal of the penis may be closed, and this new canal will serve only for accomplishing ejaculation.

*Vesical Calculus.*—Price<sup>23</sup> stated that vesical calculus is rather common in Shantung Province. His report is based on the cases of 126 patients who were admitted to the University Hospital in the last five years. Most of the patients were boys from the country, between 5 and 15 years of age, who began to have symptoms in the spring in the second to the sixth year of life. Characteristic symptoms occur in attacks of increasing length and severity, until finally there are no symptomless intermissions. The etiology of vesical calculus is obscure. Price's study of the incidence appears to lend indirect support to the theory that dietary deficiency, perhaps vitamin A deficiency, is an important causative factor. In his experience, roentgenologic examination is the most informative single diagnostic procedure for stone in the bladder. Demonstration of the presence of a stone in the bladder is not sufficient; the condition of the urethra, bladder, kidneys and body in general should be determined. If severe cystitis or evidence of renal damage is found, operation is best delayed until the condition can be improved. The preoperative, operative and postoperative treatment developed at the University Hospital was described in detail. Its essential features are: adequate preoperative treatment which is based on careful and complete diagnosis; suprapubic lithotomy, the bladder being distended with measured quantities of air; special care that the wound does not become contaminated by vesical contents; anatomic closure of all the layers of the wall of the bladder without drainage; drainage of the bladder for four or five days by means of a catheter carefully placed and securely fastened in the urethra, and attempts to restore the entire urinary tract to normal. A stone which is partly impacted in the prostatic urethra presents special problems. Suggestions are made for dealing with this sort of case.

*Foreign Bodies.*—The introduction of foreign bodies into the urinary bladder may be either intentional or accidental. Almost every known conceivable substance that the urethra can admit has been introduced into it and subsequently found in the bladder. Most commonly, Kau<sup>24</sup> found lead pencils, wire hairpins, crochet needles, rubber tubing, stems of plants, shirt buttons, shoestrings, glass rods and wire, and recently, more cases were reported in which chewing gums and paraffin wax had been introduced into the bladder. On the other hand, the foreign bodies which were accidentally introduced into the bladder were more commonly found in aged people and consisted of instruments used for the relief of urinary retention. Portions of ordinary or Pezzer catheters, glass catheters, bougies, jaws of lithotrites and similar instru-

23. Price, P. B.: Bladder Stone, Chinese M. J. 48:462 (May) 1934.

24. Kau, Z. M.: Foreign Bodies in the Urinary Bladder, Chinese M. J. 48:475 (May) 1934.

ments composed most of the foreign bodies found in this group during the last century, but with the improvement of our surgical technic and the instruments these accidents have become less frequent. There is a rare group of foreign bodies that may gain entrance into the bladder through ulceration of the vesical wall. These foreign bodies are usually situated or get lodged in the perivesical space; they consist of gauze sponges overlooked at operation, sequestrums from osteomyelitis of pelvic bones, fragments of shells and bullets. As a result of mechanical irritation by a foreign body, infection of the bladder sooner or later takes place. Cystitis, therefore, is a common complication of the presence of a foreign body in the bladder, especially in the chronic and latent cases. With infection, phosphatic incrustation ensues and a stone develops, with the foreign body as the nucleus. Foreign bodies which have rough or irregular surfaces are more susceptible to phosphatic incrustation; this is practically absent or the process goes on slowly in the case of smooth objects such as glass or wax. Foreign bodies which have sharp pointed ends, such as needles and pins, are liable to produce ulceration of the vesical wall and secondary perforation. Sometimes they may escape through this perforation and be discharged to the peritoneal cavity, perivesical space, rectum or vagina. On account of the irritation of the bladder and the accompanying cystitis, disturbances in the act of urination dominate the clinical picture, though in certain cases the foreign body may remain latent and symptomless. Frequency of micturition, painful urination, urgency and tenesmus are the usual symptoms presented by these patients. Hematuria and pyuria are almost always present at one time or another. Acute or chronic urinary retention and incontinence of urine may develop if the foreign body is impacted in the vesical orifice. Pain may be referred to the tip of the penis or to the perineal region. In fact, the symptoms are more or less similar to those of vesical calculus. The treatment depends on the nature and shape of the foreign body. A careful cystoscopic and roentgenologic examination is essential before treatment. In general, it may be described under two headings, the nonsurgical and the surgical. In the nonoperative treatment, foreign bodies, such as catheters, filiforms, rubber tubing, stems of plants, chewing gum, wax and needles may be removed through the operating cystoscope, Young's cystoscope rongeur, the observation lithotrite or Kelly's hollow tube cystoscope with alligator forceps. Care must be taken in removing sharp pointed objects, especially needles, for rupture or injury to the bladder or urethra may occur otherwise. Surgical removal by means of suprapubic cystostomy is indicated whenever nonoperative treatment fails or in the absence of special instruments.

*Fistula.*—Elaut<sup>25</sup> reported a new method of treatment of vesico-vaginal fistulas which meets the requirements better than any other method in cases in which there has been extensive loss of substance. It has been successfully used in two cases.

A method, to be satisfactory, must place the restored wall of the bladder beyond the reach of the least traction that might compromise its continuity; hence the catheter tube used for drainage of urine must be so placed that it does not come in contact with the surface of the vesical wound. It also must protect the sutured wall from the corrosive action of the urine; it must therefore effect drainage at the lowest part of the bladder, so that the bladder may be emptied completely. These conditions are fulfilled in Elaut's transcervical drainage, which is carried out through the anterior wall of the cervix uteri by means of a specially devised curved metal tube which conducts the urine through the vagina and across the perineum into the urinal. When the tube is once in place, the fistula is closed by the standard procedure after the making of a duplication of the vesicovaginal partition. To understand the basis of this method, it is necessary to observe the anatomic relations of the bladder and the cervix. The important points to study are the distance between the anterior vaginal culdesac and the peritoneum of the vesico-uterine space, the point of the bladder that is lowest when the patient is recumbent, the point of contact of the bladder with the cervix, the vessels that might be injured during manipulations inherent in the drainage and the situation of the ureters with reference to the tract of the tunnel. In carrying out his studies on cadavers, Elaut took account of the fact that the fistulous bladder must be regarded as empty. He found that the distance between the vagina and the peritoneum, while varying in different persons, averaged 35 mm. in normal subjects during the sexual period of life. In cases of metritis, perimetritis and parametritis, its length may be 40, 50 or 60 mm., as the result of the enlargement of the uterus caused by inflammation. It is at the level of this region that the bladder and the uterus are in contact with one another at the vesico-uterine partition. The peritoneum lining the space between the uterus and the bladder posterior to this partition is the equivalent in the female of Denonvillier's fascia. It is worthy of note that there is no fat in this space. The only point of contact of the uterus with the bladder is at the cervix. Even when the bladder is empty, the tract making contact is never less than 25 mm. long under normal conditions. On the vesical side of the partition, the contact is in the region in which the greatest transverse diameter is found; this diameter is constant whether the bladder is full or empty;

25. Elaut, L.: De la derivation transcervicale de l'urine dans la cure des fistules vesico-vaginales, *J. d'urol.* 37:21 (Jan.) 1934.



it runs from one lateral recess to the other, and it is at about the middle of this tract that the point of contact is to be sought. This line, which constitutes the postero-inferior border of the vesical cavity, is about 40 mm. from the line joining the ureteral meatuses. By restricting the incision rigorously to the median line, one can be absolutely certain that the drainage tube will puncture no vessel, however small. The operation is divided into two stages: exposure of the vagina and the placing of the drainage tube. The exposure must be as wide as possible, and in some cases it may be necessary to incise the perineum. To admit the tube, the cervix may sometimes have to be slightly dilated.

*Vesical Pressure.*—Watkins<sup>26</sup> investigated the condition of the detrusor muscle in cases of injury to the lower part of the spine by estimating the vesical pressure. For comparison, studies were made of the normally innervated bladder, and as a result Watkins concluded that although definite information concerning the condition of the innervation of the bladder can be obtained by making careful estimations of the vesical pressure most of the information can be derived from simpler measures and from clinical observations.

A vertical glass tube, 4 mm. in internal diameter, was used as a water manometer. It was connected by a T-tube with a reservoir filled with a 1:4,000 solution of mercuric oxycyanide and an inlying catheter. Fifty cubic centimeters of fluid was introduced, and readings were taken at the first sensation of filling, at the first attempt at urination, either from actual contraction of the detrusor muscle or from abdominal straining, and then after each further addition of 50 cc. of fluid. The results in 24 cases in which there was normal innervation of the bladder are discussed and compared with those obtained by other investigators.

Watkins concluded that with the use of the water manometer it should be simple to differentiate between rises of pressure resulting from abdominal straining and those which result from contraction of the detrusor muscle. Furthermore, it should be possible to demonstrate contraction of the detrusor muscle at any observation on a normally innervated bladder, and such contraction should cause a pressure of about 150 cm. of water or more, which is approximately twice as great as can be caused by abdominal straining alone.

Three cases were studied; these were cases of urinary retention from lesions of the spinal cord with disturbance of the sacral segments. Important evidence can be obtained by readings of vesical pressure, particularly in regard to contraction of the detrusor muscle, while the

---

26. Watkins, K. H.: The Clinical Value of Bladder Pressure Estimations, *Brit. J. Urol.* 6:104 (June) 1934.

nature of the pressure curve "at rest" and the point of first sensation are of much less value.

However, it is doubtful if the same information cannot be obtained by simple clinical methods. At cystoscopic examination it is possible to determine the point of first sensation and the capacity of the bladder. By watching the urinary stream after excluding the presence of obstruction, it is possible to determine the presence of powerful contraction of the detrusor muscle. If the stream is forcible, of wide caliber and continuous, evacuation must be the result of contraction. In a paralyzed bladder there are much straining, poor force, narrow caliber and interruptions coincident with the taking of a deep breath, which hinder abdominal action and straining.

At the present time it does not seem justifiable to make any very vigorous claims for the introduction into routine clinical practice of a method which provides little more information than can be derived by simpler methods.

*(To be Concluded)*

## Correspondence

---

### CONTINUOUS INTRAVENOUS INJECTION

*To the Editor:*—In the April issue of the ARCHIVES OF SURGERY (30:685, 1935) there is an article entitled "Experimental Pulmonary Embolism Associated with Venoclysis" by Mervin J. Rumold, of Kansas City, which seems to discredit the use of continuous intravenous injections. For several years I have been advocating and using continuous intravenous injections, particularly in connection with surgical procedures, and I have written several articles on the subject.

The experiments of Dr. Rumold appear to have been carefully performed, but in my experience his conclusions do not seem applicable to clinical work for the following reasons:

1. The vein used by Dr. Rumold in all of his experiments (listed in the six tables) was the external jugular vein in a dog, except in 2 experiments in which the saphenous vein was used. In a dog the external jugular vein is large and practically supplants the internal jugular vein, which is always small and almost negligible in function. The total number of dogs experimented on was 19. After each of the 19 experiments either pulmonary infarcts or pulmonary thrombi resulted, usually both. A clot in the large external jugular vein of a dog would probably be quickly transported to the lung because of the size of the vein and the very short and direct communication with the vena cava. I know of no clinical instance in which a continuous intravenous injection has ever been given through the jugular vein. In the 2 experiments in which the saphenous vein was used, it is said that "Considerable difficulty was encountered in keeping the dogs quiet." On the whole, then, so far as the vein is concerned the conditions that obtained in the experimental work of Dr. Rumold are quite different from those in the clinical use of intravenous methods. Even in the 2 experiments in which the saphenous vein was used, the dogs obviously could not be well restrained. Clinically, in continuous intravenous infusion, or so-called venoclysis, the arm or leg into which the solution flows is kept still, usually by a small splint. If a patient were to use the arm or leg through which continuous intravenous injection was being given, a clot not only would be more readily formed from injury to the intima of the vein but would be more readily forced into the circulation.

2. The solution that was used in almost all of Dr. Rumold's experiments was a 10 per cent solution of dextrose. As was shown by Matas in his original contribution on continuous intravenous injections, a 5 per cent solution of dextrose is about isotonic with the blood. Ringer's solution is known to contain most of the important electrolytes of the blood in the approximate proportion in which they are found in the blood serum. A 10 per cent solution of dextrose is distinctly irritating to the vein, though doubtless it can be employed for a few hours with comparative safety. When it is desired to stimulate the function of the kidneys or to reduce edema, a 10 per cent solution of dextrose may be used, but the fact that the stronger solutions of dextrose are one of the remedies for sclerosing varicose veins shows it is much more likely to cause injury to the veins than the isotonic 5 per cent solution. Naturally, the insertion of a needle, and still more of a cannula, into a vein may induce a clot at the point of trauma. That this is not a frequent or serious occurrence, however, is shown by the common and innocuous practice of removing the blood from a vein for a Wassermann test or

by the intravenous administration of various drugs. Rarely is the vein occluded in these instances, or, if it is occluded, the smaller caliber of the vein and the distance from the vena cava make it probable that the clot will become adherent to the intima and eventually be absorbed. Often veins that have been occluded with thrombi resolve and become permeable again. It is well known that even in the extensive thrombosis that occurs after phlebitis pulmonary emboli are very uncommon, though they do occur. The injection of sclerosing material into large varicose veins seems to afford a much more fertile field for pulmonary emboli than could possibly occur from the slow injection of an isotonic solution into a small vein, yet such an occurrence is rare.

3. The employment of the apparatus which Dr. Rumold illustrates is distinctly favorable for pulmonary thrombosis. The so-called Murphy "drip method" of administering fluid into the rectum is convenient for determining the rate of flow, and any air that is carried into the rectum is harmless. Why this procedure should be adopted for intravenous injection, however, I have never been able to understand, because it is well known that the injection of air in any considerable quantity into the venous system is injurious and often fatal. It may plug a branch of the pulmonary arteries and form a thrombus, while the original cause of the thrombus—the air—may be readily overlooked in the necropsy. This drip method seems to have for its only recommendation the fact that the rate of injection can be gaged. Even this advantage is more apparent than real. By the use of a narrow buret containing about 500 cc. of solution, the flow of the solution can be regulated fairly accurately so that it can be cut down to as low as 50 cc. an hour with considerable accuracy by quickly noting the changing level of the fluid on the narrow buret. In the drip method, however, the drops must be counted as the pulse is counted, and the size of the drops may not always be the same. If in the glass drip apparatus there is an aperture for air, as in proctoclysis, the air can, of course, readily enter this space, but even if there is no such aperture the rate of flow below the apparatus may become greater than the supply above to the apparatus, which may result in the suction of air into the blood stream. If the patient or animal vomits, strains or becomes congested, the rate of absorption of the intravenous injection would be temporarily slowed down because of the venous back pressure, but when this passes off and the respirations become more rapid the rate of venous flow is increased, and it is easily conceivable that some air may be sucked in because the rate of supply by the drip method is fixed. Even though there may be no direct communication with the outside air, a partial vacuum in the drip apparatus may be induced and air aspirated into the vein. An air bubble coming into the circulation and speeded along by the force of the intravenous injection as well as by the flow of the venous current may readily pass through the right auricle and ventricle and into the pulmonary circulation without being sufficiently large to disturb the action of the heart.

4. Experimental work on dogs is interesting and often uncovers many valuable points, but the results cannot always be directly transferred to man. Thus, for instance, the Koontz fascia lata of the ox seems to have been almost perfect in dogs and is incorporated into the tissues, but in human beings, in my own experience with it, it has been unsatisfactory. In 2 cases the abdominal wound broke open, once nine days and once six days after the operation, and I have had other unfortunate experiences with it. The fascia was recovered in these cases and was shown to be disintegrated.

During the last five years continuous intravenous injection of a 5 per cent solution of dextrose in Ringer's solution has been used at St. Elizabeth's Hospital, Richmond, Va., in about 2,500 patients, the length of the period of administration

varying from three hours to four days. In many of these patients it was used several times. I believe that it occasionally was life-saving. In this period of five years 6,237 patients were admitted to St. Elizabeth's Hospital, and there were 4 deaths from pulmonary embolism. One of the patients, who received 1,000 cc. of a 5 per cent solution of dextrose in Ringer's solution the first day after operation, which was done for acute gangrenous appendicitis, died suddenly seventeen days later while he was up in a chair. Another patient, who was operated on for vesical stone, suprapubic cystotomy being done, received 500 cc. of a 5 per cent solution of dextrose in Ringer's solution the day of operation and died suddenly of pulmonary embolism eighteen days later. A third patient received about 8,000 cc. of a 5 per cent solution of dextrose in Ringer's solution over a period of about three days after gastro-enterostomy and died of pulmonary embolism sixteen days after the operation. This is the only case in which venoclysis can be reasonably considered as a probably causative factor. The fourth patient, who had an exploratory operation followed by roentgen treatments for carcinoma of the ovary with metastases, died two weeks after the operation from pulmonary embolism. She had received no intravenous injection of any kind.

The incidence of pulmonary embolus over this five year period appears to be no greater than that noted when continuous intravenous injection of dextrose is not used. The comparison of the results of venoclysis in 2,500 clinical cases with those of Dr. Rumold's 19 experiments in dogs becomes obvious. I regard continuous administration of a 5 per cent solution of dextrose in Ringer's solution when properly given as one of the greatest aids in many cases, and I should not willingly dispense with it except after some convincing demonstration of its injurious effects.

J. SHELTON HORSLEY, M.D., Richmond, Va.

# ARCHIVES OF SURGERY

VOLUME 39

JUNE 1935

NUMBER 6

## TUMOR OF THE NEUROMYO-ARTERIAL GLOMUS

### REPORT OF CASES

VICTOR RAISMAN, M.D.

AND

LEO MAYER, M.D.

NEW YORK

In this article we shall report three cases of tumor of the neuromyo-arterial glomus, an entity as yet undescribed in the American literature, and present a description of this tumor, with a tabulation of all reported cases.

### REPORT OF CASES

CASE 1.—E. B., a woman 28 years old, complained of pain in the tip of the third finger of the right hand. This pain began twelve years previously when a drawer was slammed on the finger. Shortly after the accident a blue spot, the size of a pinhead, appeared under the nail at about its center, and the tip of the finger remained painful for many weeks. In the years that followed, slight traumas to the nail caused an exaggerated amount of pain. Also, the finger became rather painful during ordinary cold weather, and if the temperature fell to the freezing point, the pain became almost unbearable, necessitating the wearing of a heavy fleece-lined glove. At times pain appeared spontaneously or possibly after unnoticed slight traumas. Occasionally it radiated up the forearm to the internal condyle of the humerus, following approximately the course of the median nerve. During the two years prior to examination the pain became more severe and the attacks more frequent. The bluish spot remained unchanged, and in all other respects the nail and subungual tissue appeared normal, except that digital pressure on the nail on its ulnar side or pressure on the tip of the finger near the nail caused pain. The pain was more severe during the night.

The patient had consulted several surgeons in order to obtain relief. None had been able to make a diagnosis or even been willing to consider an exploration. A diagnosis of subungual calculus was suggested, but since an x-ray photograph, carefully taken for soft tissue detail, failed to reveal areas of increased density, operation was not advised. When the patient consulted us in July 1933, we noted the following physical signs: Near the center of the finger-nail was an area of bluish discoloration about  $\frac{1}{8}$  inch (0.32 cm.) in diameter (fig. 1A). When pressure was made against the tip of the nail sufficient to cause a blanching of most of the nail, the bluish area was made to stand out in sharper contrast. Gentle pressure applied locally to the region of the discoloration or to the tip of the nail caused pain. There was no irregularity in the growth of the nail, which was well formed and smooth, even under the magnifying glass. No disturbance of circulation or of sensation could be found. The pulp of the finger was normal. Nothing found in the general examination could explain the local pain and tenderness. An x-ray picture showed no abnormality of the bone.

From the Orthopedic Service of Dr. Leo Mayer, Hospital for Joint Diseases.

Two diagnoses were considered: a subungual papilloma and a chronic low-grade infection of the bone with secondary inflammation of the subungual tissues. That we had no inkling of the true nature of the pathologic process was due entirely to our ignorance of glomal tumors, for had we known of Masson's work we could have recognized the condition at a glance.

Fortunately, despite our diagnostic errors, we advised operative exploration, and accordingly the patient was admitted to the Hospital for Joint Diseases in July 1933. Under local anesthesia obtained with 1 per cent procaine hydrochloride, to block the sensory nerves at the base of the finger, the operation was performed as follows:

A portion of the nail was removed piecemeal with a small rongeur, exposing the bluish area visible through the translucent nail. The discoloration seemed to be due to a thinning of the subungual tissues. It extended over an area about  $\frac{1}{4}$  inch (0.64 cm.) long and  $\frac{1}{8}$  inch (0.32 cm.) wide (fig. 1 *B*). The tissue here looked thin and slightly bluish. When the superficial layer was removed with a knife, a peculiar tissue was exposed which had the appearance of partly fluidified fat. No enveloping capsule was visible. The tissue was gently curetted away until the dorsal surface of the terminal phalanx was exposed. This was found slightly roughened, and a minute crater was noted on its surface. The surface of the bone was gently curetted until all roughening had been removed. The area left by the removal of the fluidified fat was then packed with petrolatum-treated gauze, and a dry dressing was applied.

The postoperative healing of the wound was uneventful, and the nail grew back perfectly. Approximately one week after the operation, the patient complained of spontaneous pains similar to those which she had previously, but in the course of the next few days these disappeared, and since that time she has been free from pain. The cold experienced during the following winter caused no pain, ordinary pressure on the nail causes no tenderness, and no spontaneous attacks have occurred. Severe pressure on the nail still causes slight pain, but this is far less than before and is becoming less with each succeeding month.

Even at the time of the operation we were still in complete ignorance of the true nature of the lesion. We made a tentative diagnosis of subungual chronic infection associated with mild osteitis and had a specimen of the peculiar fatty-like tissue sectioned by the laboratory. To our amazement a report of basal cell carcinoma was returned. This seemed so at variance with the clinical course and symptoms that we requested further pathologic consultation. Prof. James Ewing dispelled our doubts and put us on the right track by informing us that the tissue was neither carcinoma nor chronic infection but a typical glomal tumor.

We are indebted to Dr. H. L. Jaffe, pathologist of the Hospital for Joint Diseases, for the following description of the microscopic appearance of the tumor (fig. 2).

"The section shows sheets of endothelioid or epithelioid-like cells. These cells are fairly large and polyhedral and contain round vesicular nuclei (*A*). All the cells are hyperchromatic. Numerous vascular spaces are observed between the sheets of cells, and these spaces are lined by more flattened cells (*B*). The section also reveals scattered areas containing more or less mucoid neural elements (*C*). The cellular picture displays a general uniformity" (fig. 2).

As no mention of this unusual type of neoplasm had been made in American medical journals, and because our colleagues revealed almost universal ignorance relative to it, a thorough review of the for-

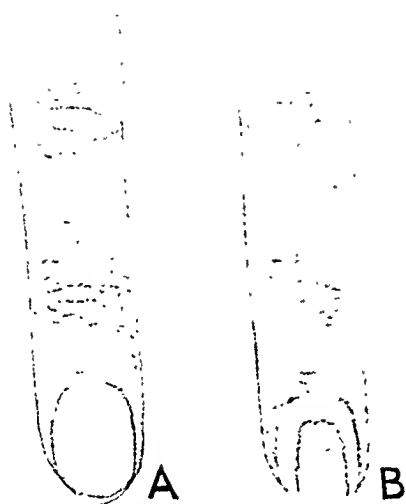


Fig. 1.—The middle finger of patient E. B.: *A*, showing the characteristic appearance of a subungual glomai tumor; *B*, at the time of operation, when a portion of the nail had been removed preparatory to excision of the tumor.





eign literature was made so that we might present a comprehensive view of the subject.

During the course of our study cases 2 and 3 were brought to our attention. In the first of these Dr. Louis Carp of the Hospital for Joint Diseases operated; in the second, Dr. Milton Friedman of the Newark Beth Israel Hospital.

CASE 2.—R. L., a woman aged 47, was admitted to the Hospital for Joint Diseases on July 17, 1933, in the surgical service of Dr. P. Grausman, with the follow-

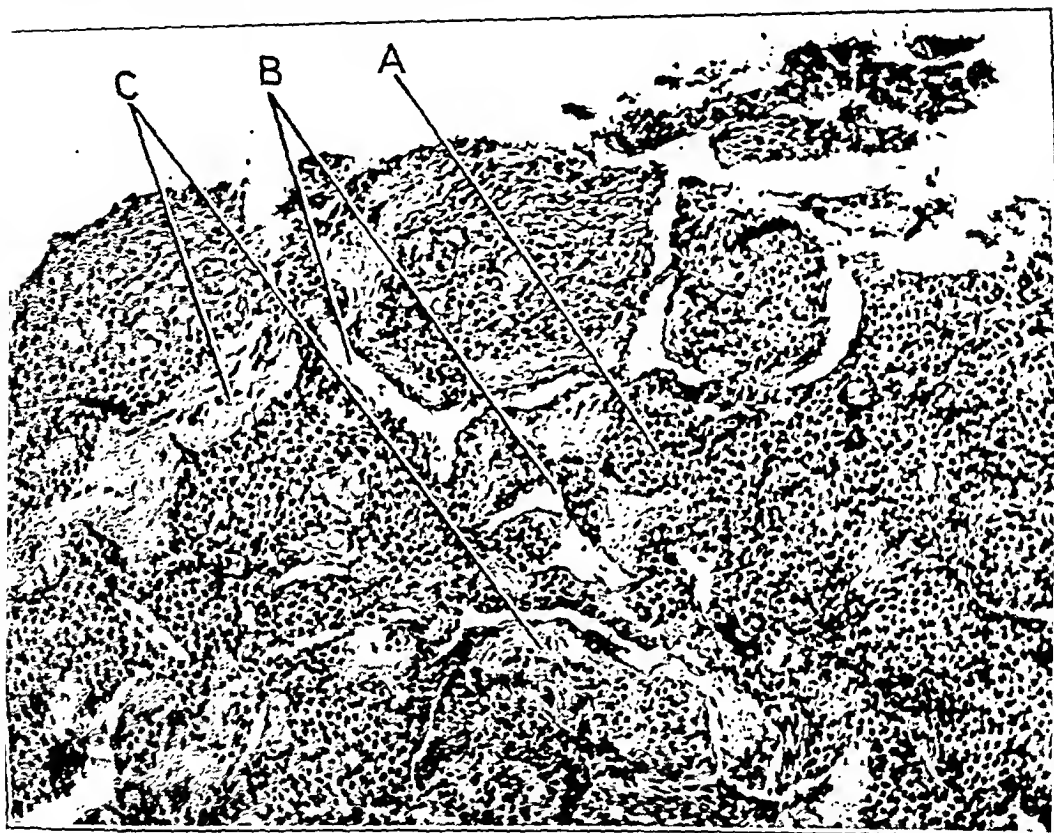


Fig. 2.—Microscopic section of the glomus tumor removed from patient E. B.;  $\times 150$ : A, endothelioid or epithelioid-like cells containing round vesicular nuclei; B, vascular spaces lined with flat cells; C, muroid areas representing neural elements of the glomus.

ing complaints: first, a small growth at the tip of the left little finger of eighteen months' duration; second, pain in the left arm, slight for sixteen years, but severe for the past three months. She had had three attacks, each lasting from two to three days, in which pain radiated upward from the finger to the heart and caused a cramplike sensation in that region. There was no history of injury to the finger. The mass had been enlarging very slowly.

On examination, the volar and posterolateral aspects of the base of the terminal phalanx of the left little finger showed a bony-hard swelling the size of a large

pea, apparently attached to the bone. The contour was regular, and the area was tender to touch. Motions of the finger were normal, and there was no adenopathy or other sign of inflammation. The x-ray photograph was normal except for a very slight crater-like defect in the cortex beneath the tumor.

At operation on July 18, a 2 cm. lateral curvilinear incision was made into the distal anterior closed space. Here was found a whitish rounded mass of moderate density, about 1 cm. in diameter, loosely embedded in the hollow of the phalanx, as shown on roentgen examination. The mass was removed by sharp dissection and the incision closed without drainage. Healing was uneventful. The pain disappeared and has not recurred.



Fig. 3.—Microscopic section of a glomal tumor removed from patient R. L.;  $\times 150$ : *A*, vascular spaces lined by flattened endothelium; *B*, vascular spaces surrounded by cells with reticular pale blue-staining cytoplasm; *C*, neural elements.

An operative diagnosis of neuroma was made, but the report from the pathologic laboratory indicated that the growth was a typical glomal tumor closely resembling that removed by us two weeks before.

The microscopic report (Dr. Jaffe) was as follows (fig. 3): "There are numerous small vascular spaces. The walls of some of these vascular spaces are made up only of flattened endothelium (*A*), but in other spaces the lining endothelium is surrounded by a layer of cells of varying thickness (*B*). These perivascular cells are of moderate size with reticular pale blue-staining cytoplasm and mostly oval deeply staining nuclei with nucleoli. Between these vascular spaces

there are some areas containing clear, more or less structureless matter. In other areas there is an extremely loosely woven mesh of what appear to be neural elements (C)."

Dr. Friedman's patient complained of a tumor of the terminal phalanx of a finger, but unlike the tumors in the first two cases, this was of recent origin and caused no pain.

CASE 3.—C. O., a woman aged 35, noted a small reddish tumor near the tip of the right ring finger, which began bleeding one week after its appearance in April 1933 and continued to bleed intermittently for three months, until she consulted her physician, Dr. Henry Kessler, who referred her to Dr. Friedman. His examination disclosed on the lateral aspect of the tip of the right fourth finger, a red hemangiomatic tumor, 8 mm. in diameter, raised 1 mm. above the line of the skin and extending down into the skin approximately 4 mm. It was not tender. On the surface was a small clot of blood. The border of the tumor was firm, thin, not raised. The results of the physical examination were otherwise negative. The tumor was removed on June 17 by endothermy under local anesthesia. Microscopic examination showed a typical glomal tumor closely resembling the tumors shown in figures 2 and 3. The wound healed without complication, and there has been no recurrence of the tumor.

Tumor of the neuromyo-arterial glomus, to give this tiny entity its full name, was originally described in its present complete form by Masson of Strasbourg, France, in 1924. He based his report on researches and on thorough microscopic studies of the tissues obtained from two subungual tumors presented clinically in 1922, by Barré of Strasbourg. After thorough histologic examination of the tissues, particularly those prepared with his special nerve stains, Masson arrived at the following conclusion: These tumors are benign outgrowths of a structure normally present in the skin and subcutaneous tissue of the entire body. This structure has in all probability been incompletely described under the name of "organ of Ruffini." From the histologic description presented in the following paragraph, he concluded that these structures which he called "neuromyo-arterial glomus bodies" were, as the result of their complicated vascular and neurogenous elements, regulators of the blood supply of the capillaries and arterioles of the skin and thus indirectly regulators of the temperature of the skin. He concluded that the tumors which he had been called on to diagnose were hardly more than enlargements, of the normal glomal bodies, but with greater disorder of the elements, so that their relative proportions varied from case to case.

The following description is a translation from an article on glomal tumors by Hopf of Bern, Switzerland, in which he paraphrases Masson's description of the normal neuromyo-arterial glomus. Owing to its brevity it is given rather than the lengthy original of Masson.

An afferent arteriole carrying blood from the interior of the body forms the major part of the glomus by dividing into from two to four thick-walled branches

with narrow lumens. From two to six vasa efferentia with wide lumens and much blood complete the glomus and unite it to the venous capillaries and veins of the skin. The thickened wall of the afferent arteriolar branches forms the major histologic feature of these bodies. Their lumens are narrow and empty only because of the absence of the "elastica interna," and collapse unless special precautions are taken. The endothelium consists of large cells with homogeneous protoplasm and large nuclei full of chromatin. Next to the endothelium are four or five layers of spindle cells arranged circularly. These cells are short and thick, with oval nuclei. On the periphery of their lightly staining protoplasm are myofibrillae, which are found in greater profusion nearer the endothelium than away from it. This circular layer of muscle fibers forms one half of the thickness of the wall. The other half, not sharply demarcated from it, consists of irregularly placed long pale cells with oval nuclei, and others which are larger and more regular and look like epithelioid cells. The former are thickened opposite the nuclei and send out, as ganglion cells do, protoplasmic projections which often unite on the periphery to compact bundles of fibers, and form a network which encircles the arterioles. They are called nonmyelinated nerve fibers by Masson because they have thin collagenous sheaths and some rodlike nuclei. These fibers are in communication with the much less well constructed network of periarterial sympathetic fibers of the afferent artery. Between the cells which form the wall of the vessel are some very fine collagenous fibers and also a few elastic fibers. The structure of the walls of these vessels is similar to that of a normal artery, but with the characteristic changes due to the local differentiation. The walls of these arterioles form a unified neurovascular system called by Masson the "neuromyo-arterial glomus."

Masson's original article on subungual glomus tumors was followed by the report of two similar cases by Martin and Dechaume in 1925. In 1927, Masson and Gery and Prodanoff widened the location of the lesion by reporting cases in other parts of the body. To the time of the present report twenty-six cases have been described. Grieg of Edinburgh in 1928 pointed out that this new entity probably coincides with the condition known in the older literature as "painful subcutaneous tubercle." Hopf's article in 1930 pointed out a probable similarity of the condition to that in other cases reported in the literature under different names. We have collected all reports of proved cases of glomal tumor and also those we could obtain from the older literature dealing with conditions which, while differently diagnosed, appear to have been similar clinically and pathologically (so far as the pathologic picture is described in the original articles) and appended these to our list as probable instances of glomal tumor.

#### CASES OF TUMOR PATHOLOGICALLY PROVED TO BE GLOMAL TUMOR

*Masson, 1924.*—CASE 1.—An 18 year old girl had complained of pain in the left middle finger for five years. The pain occurred several weeks after an injury to the finger-nail when a desk drawer was slammed on it. The pain had gradually become worse and at times was excruciating. It radiated up the arm to the shoulder and then down the body as far as the hip of the same side. There was a constant dull pain, with exacerbations occurring spontaneously and relieved somewhat by cold water. Examination showed a bluish spot under the nail, which was

otherwise normal except for the marked tenderness to pressure. Slight atrophy of the arm and Horner's syndrome on the same side were discovered. Skin tests showed increased warmth and hyperesthesia on the same side. No evidence of a lesion of the central nervous system could be found by spinal tap. A partial section of the sensory nerves to the hand gave only temporary relief. Finally Barré removed the nail, and a pea-sized subungual tumor was discovered and easily removed. Postoperatively the patient had considerable pain for two days and then gradual relief coupled with the disappearance of Horner's syndrome and the sensory changes. Six months later she was completely cured.

CASE 2.—A man complained of lancinating pains in his left index finger for thirty years. There was no radiation of the pains nor any history of trauma. The pains were increasing. Exacerbations were produced by cold and relieved by heat, so that the patient had to wear a glove constantly. Examination showed a bluish spot under the nail, and the latter was slightly raised centrally. Encouraged by the first case, Barré removed the nail and discovered a similar pea-sized tumor. Complete relief of the symptoms ensued the day after the operation.

CASE 3.—A 23 year old nurse had had increasing pain in the nail of the index finger for six years. The nail was removed sufficiently to enable Barré to excise a subungual tumor, with resultant complete cure.

*Martin and Dechanne, 1925.*—CASE 4.—A 40 year old woman had a small tumor under the nail which lifted the nail somewhat, and which had developed following a slight trauma. Removal of the tumor cured the condition, which has not recurred.

CASE 5.—A 70 year old woman had a subungual tumor which developed following slight trauma to the nail twenty-five years previously. There were spontaneous pains and marked tenderness to pressure. Removal produced complete cure.

*Masson and Gery, 1927.*—These authors were the first to publish a report of cases of glomal tumor outside of the subungual region.

CASE 6.—An 82 year old man had had a pea-sized tumor in the subcutaneous tissues of the right thigh for ten years. This caused constant pain which became worse till removal of the tumor produced a complete cure.

CASE 7.—A middle-aged man had suffered an injury fifteen years previously, and following this a small tumor developed in the thigh, which caused marked pains. Removal gave complete cure.

CASE 8.—In a pathologic collection Masson and Gery found a tumor which had been removed from a 69 year old man.

CASE 9.—In a pathologic collection Masson and Gery found a small tumor from the subcutaneous tissue of the forearm.

*Prodanoff, 1927.*—CASE 10.—A 68 year old man had had an injury twenty-two years previously. Nine years later, pains developed in his left thigh, which became constantly worse, so that even the contact of his trousers on the tender area was unbearable. As he walked around he kept his hand in his pocket to prevent contact of the clothes with the skin at that point. At operation a small tumor was found on the inner side of the thigh. It was round, soft, red, 11 mm. in diameter, and its removal was followed by complete cure.

*Nicod, 1927.*—CASE 11.—A 31 year old woman, had suffered pains under the left thumb-nail for four years with no known etiologic factors. The pains were lancinating. The condition was thought to be due to a foreign body, which was probed for but nothing found. The pains were intermittent, but present every

day, radiating up the arm to the shoulder. Neurologists thought that the patient was suffering from a tumor of the spinal cord. Finally a tumor was seen under the nail and removed, with complete cure. The tumor was small, soft and red.

*Bonnet, 1927.*—CASE 12.—A 46 year old woman had had pains under the nail of the right little finger since the age of 10. The nail was extremely tender. The pains were relieved by cold. They had been severe for many years, during which the patient had had many different types of nonsurgical therapy without relief. The patient was quite willing to have the arm amputated in order to obtain relief. An x-ray photograph showed a slight hollowing of the distal phalanx. At operation the distal phalanx was disarticulated and complete relief obtained. Pathologic examination showed a glomal tumor in the subungual tissue.

*Greig, 1928.*—CASE 13.—A 42 year old man had had three small nodules in the subcutaneous tissue of the right deltoid region for ten years following an injury. These tumors were painful on pressure and painful spontaneously or when the weather changed. Excision brought about a cure.

CASE 14.—A 33 year old woman had had a nodule in the left calf for eight years, which was tender to pressure, painful when the temperature changed from cold to hot and vice versa, and also painful for about an hour if she stood up after sitting a long while. Excision gave cure.

*Lortat-Jacob and Brosse, 1928.*—CASE 15.—A 41 year old woman had had pain in the left hand for sixteen years, not following trauma. At first there had been a sensation of tingling; gradually a burning sensation developed which became severe and, though felt in the entire hand, appeared to come from the tip of the fourth finger. Finally, pains developed which radiated up the entire arm. The pains were decreased by immersion of the hand in warm water. Soon a bluish spot appeared under the nail, and from then on there occurred frequent crises of acute pain brought on by pressure on the nail or by cold, so that she was forced to wear a glove constantly. Four years after the onset, the nail was removed to cauterize the bluish spot but to no avail. For three years there had been a slight elevation of the nail, making it more convex. Besides the bluish spot and the convexity of the nail, the findings were negative. Removal of the nail disclosed a subungual tumor, which was removed, with complete relief.

*Ianichewski and Lebel, 1928.*—CASE 16.—A 50 year old woman had had pains in the left fourth finger for eighteen years, not following any trauma. The pains were increased by cold and dampness and relieved by heat. The finger was extremely tender. The patient was unable to work and walked around wearing a fur glove. A nerve block was attempted, with temporary relief. Examination showed a bluish spot in the palmar aspect of the finger underlying which was a tumor the size of a pea. Its removal produced complete cure.

*Hopf, 1930.*—CASE 17.—A 50 year old woman had had spontaneous pain over the left acromion for ten years, which increased under pressure, at night and on changes of weather. A subcutaneous tumor, bluish, the size of a pea, could be palpated. This was removed, and complete cure followed.

CASE 18.—A 78 year old woman had had a slowly growing tumor in the palmar aponeurosis for many years, which was not painful, but tender, and bluish. Removal resulted in complete cure.

CASE 19.—A 47 year old man had had a small, slowly growing tumor in the left leg for many years. This was painful and blue. On removal it was soft but sharply defined. Complete cure followed.

CASE 20.—A 65 year old man had had a painful tumor in the thigh for four years. Removal yielded cure.

*Picard, 1931.*—CASE 21.—A 49 year old merchant had had a slowly growing enlargement of the left index finger just proximal to the nail for a long time. There were no subjective symptoms, no pains. The condition did not follow any trauma. Operation revealed three small tumors. No recurrences were apparent sixteen months later.

*Dufont, 1931.*—CASE 22.—A woman complained of terrific pains in the upper extremity, and the surgeon, finding a swelling of the finger with osseous lesions on roentgen examination, decided that it was a sarcoma and disarticulated the distal phalanx.

CASE 23.—This was a specimen sent for pathologic examination without any history.

*Fernandez and Mousserat, 1931.*—CASE 24.—A 38 year old man had complained of pains in both ears for four years, during which time four or five small tumors appeared and disappeared on the helixes of the ears. These tumors were very small, superficial to the cartilage and not attached to it. The pains were spontaneous and also induced by pressure, so that the patient had great difficulty, when going to sleep, in lying in such a way that nothing touched his ears. The pains frequently radiated to the head. Under local anesthesia, the tumors were removed. During the operation much bleeding was encountered. (If it were not for the proved pathologic diagnosis, this condition would appear to be outside of our group of cases, as the tumors were bilateral, appeared and disappeared, and finally, removal was accompanied by much bleeding.)

*Costa, 1932.*—CASE 25.—A 50 year old woman had had pains in the left upper extremity for over ten years with no traumatic history. Onset occurred with tingling in the left index finger, followed later by pains as though the finger were being pierced by a needle. These lancinating pains then radiated to the shoulder and thorax. They were worse at night. They were also increased by using the hand, by changing its position, by changes of temperature and by pressure on the nail. Cold water gave some relief. Gradually the nail became lifted by a blue-red subungual tumor. There was atrophy of the muscles of the hand and forearm. Neurologic examination gave negative results, but it was difficult to examine the patient because of the extreme pain and tenderness. At operation a tumor, 12 by 5 mm., was removed, with almost immediate relief. Complete cure resulted.

*Paulian, Stefan-Papescu and Marinesco-Slatina, 1933.*—CASE 26.—A 32 year old woman had been suffering from pains and a burning sensation in the right upper extremity for a long time. These were accompanied by a feeling of warmth on the entire right side of the body and the face. A violaceous spot was found under the right third finger-nail, pressure on which reproduced these sensations. Careful reading of the cutaneous temperatures showed that areas on the right side of the body had temperatures from 1 to 2 degrees higher than those of the corresponding areas on the left side. Removal of the tumor produced cure of all symptoms.

#### PROBABLE BUT UNPROVED CASES OF GLOMAL TUMOR

*Wood, 1812.*—Wood discussed cases of "painful subcutaneous tubercles." He stated that these are tumors the size of a pea or coffee bean, found in women in the subcutaneous tissue, not adherent to the skin or deeper tissues, located most usually on the extremities, although they may be anywhere. They all cause paroxysms of pain radiating centrally, are frequently affected by changes of



temperature and are frequently bluish. They may be tender constantly or only during a painful crisis, and their removal is easy and produces complete cure.

CASE 1.—A 30 year old woman had three nodules over the *gluteus maximus* muscle. Their color was normal. There were frequent attacks of pain in this area brought on by the friction of clothes. Their removal gave complete cure.

CASE 2.—A 70 year old woman had had a tubercle at the right knee for thirteen years which made her miserable with paroxysms of pain lasting from thirty to ninety minutes. During the paroxysms the tumor was tender, but in the intervals it was not. The color was normal. Removal resulted in cure.

CASE 3.—A 28 year old woman had had a tumor on the outer side of the right leg for seven years, with paroxysms of pain during which it became bluish. The pains increased in severity. Removal produced cure.

CASE 4.—A 50 year old woman had had a tubercle in the middle of the right arm for twelve years with pain radiating to the shoulder and down to the fingers. The color was unchanged, but the nodule became tender during the paroxysms. Removal gave cure.

CASE 5.—A 29 year old woman had had a lump over the left *gastrocnemius* muscle for twelve years which grew slowly and caused shooting pains. Removal cured this condition.

CASE 6.—A 33 year old woman had a tubercle on the left forearm causing exquisite pains, which were relieved by its removal.

CASE 7.—A 57 year old woman had experienced an injury to the right calf ten years previously with resulting formation of a small nodule. This had a reddish tinge and caused pains which were increased by heat or cold. This was not operated on.

CASE 8.—A 40 year old woman had had a tumor at the right elbow for ten years. There were paroxysms of pain during which the tumor became bluish. Removal cured these symptoms.

*Paget, 1853.*—In his lectures on surgical pathology, Paget described a group of tumors which, despite their size and apparent innocuousness, were remarkable for the pain they caused. He differentiated them from fibrocellular and fibrous tumors by the pain. They were not neuromas. The majority of them were in women and rarely did a patient have more than one. They never grew over  $\frac{1}{2}$  inch (1.27 cm.) in diameter, usually lay just below the skin, had a capsule and were not adherent to any other tissues. After removal they never recurred. He referred to Wood's paper as his authority.

*Crampton, 1853.*—CASE 9.—A 16 year old girl had had frequent attacks of excruciating pain in the tip of the middle finger for three years. Removal of a small tumor, the size of a snipe shot, revealed a fibrous structure with apparently no nerve connection and produced complete cure.

*Schuh, 1862.*—This author, describing various neoplastic conditions, mentioned a case of a tumor which is called "colloid sarcoma" by Heller:

CASE 10.—A young woman had had pains in the right thumb for many years, increased by weather changes and the slightest touch. The pains radiated up the course of the median nerve. Examination showed a pinhead-sized gray spot under the nail. At operation a pea-sized tumor was removed and complete cure obtained. Clear fluid exuded from the tumor.

*Labbé and Legros, 1870.*—In discussing neuromas, Labbé and Legros mentioned the following cases:

CASE 11.—A young woman 22 years old had had a tumor on the right calf for three years, with occasional pains at that point. When she became pregnant, the tumor became very painful and very tender on direct pressure. Examination two months later showed a small bluish tumor and its removal cured all symptoms.

CASE 12.—A young woman aged 23 had had a small tumor on the right calf for five years, which became painful three years before examination. The pain increased and radiated to the foot. Removal resulted in cure.

CASE 13.—A 37 year old man had had a little tumor on the right fourth finger for about nine months, causing terrific pain, which radiated up the entire extremity. Examination showed a bluish spot. After removal of the tumor the pain disappeared.

*Tillaux, 1870.*—CASE 14.—A young woman, aged 25, had a small tumor superficially located in the upper internal quadrant of the right breast, whose cause and duration were unknown. It caused pain in the breast and right upper extremity, preventing her from sleeping and making work difficult. It was slightly tender. Removal resulted in complete cure. Although the author found adenomatous tissue, he diagnosed the growth as painful subcutaneous fibroma.

*Kolaczek, 1878.*—Writing about an entity known as angiosarcoma, Kolaczek described a tumor as follows:

CASE 15.—A 42 year old woman had had terrific pain under the nail of the right big toe for four years. A soft, gray, pea-sized tumor was removed, producing complete cure. The microscopic reports are very similar to the description of a glomal tumor.

*Monod, 1879.*—Monod described one of three cases of a condition called by Trilat "painful subcutaneous angioma":

CASE 16.—A 50 year old woman had had a tumor on the back of the right elbow for two years following an injury. The tumor was subcutaneous and not adherent. It was bluish and was very tender. It grew slowly and caused increasing pain, which was worse at night. Removal produced cure. It is stated that it was the pressure of the tumor on the adjacent nerves that caused the pain, as no nerves were found in the tumor.

*Chandelux, 1882.*—This author presented a paper on his researches into the pathology of "painful subcutaneous tubercles." He stated that these are small painful nodules found under the skin in various parts of the body which have been described innumerable times and given almost as many names. Owing to the fact that various investigators used different stains, they emphasized different factors and therefore called the tumors "fibroma," "neuroma," etc. Bruce and Paget thought that the pain depended on the patient's disposition.

CASE 17.—A 54 year old man had had a pea-sized tumor on the right forearm for twenty-five years with lancinating pain radiating from it, either following pressure or spontaneously. The tumor grew slowly and only to a slight extent. The patient found that strong compression on the entire arm by a bracelet at that level gave relief. There was a reddish discoloration of the skin. Removal resulted in complete cure. The pathology seemed very similar to that of glomal tumor.

CASE 18.—A 43 year old woman had had a small tumor in the right cubital fossa for six years. The pain was terrific and occurred spontaneously or following

pressure. The tumor was felt subcutaneously, and there was a bluish color to the skin. Removal cured the condition. The tumor had a microscopic appearance similar to that in the previous case.

CASE 19.—A 16 year old girl had had pain in the left fourth finger under the nail for two years. The pain gradually became intense, so that the patient could not sleep. The nail was raised slightly. A reddish pea-sized tumor was removed with resultant cure.

CASE 20.—A 46 year old woman had had pains in the right fourth finger in the palmar aspect of its first phalanx for four years. This pain radiated up to the shoulder and down to the abdomen. A pea-sized tumor with no decided color changes was removed, and this cured all the symptoms.

In conclusion, Chandelux expressed the belief that such tumors are painful, not because they are neuromas, but because they compress nerve ends by their growth. They are vascular and therefore cause coloration of the skin, and they have a varied pathology. The spontaneous pains occur when the turgescent vessels expand and press on the nerve endings.

Krasko, 1887.—This author described two subungual tumors and the characteristics of such tumors. They are benign, have a slow growth under the nail, hollow out the underlying distal phalanx, produce a blue discoloration, but have a gray-red color themselves.

CASE 21.—A 42 year old woman had had a pain under the left middle finger-nail for twelve years following an injury. There was a blue spot under the nail. The finger was amputated and revealed a gray and red pea-sized subungual tumor, which was not attached to the bone, and which presented a microscopic picture very similar to that of a glomal tumor.

CASE 22.—A woman in the forties had had terrific pain in the left thumb for twenty years. There were marked tenderness to pressure and radiation of pain to the shoulder. A pale pea-sized tumor was easily removed from the subungual region, with complete subsidence of all symptoms by the following morning. The microscopic picture was the same as that in case 21.

Chisholm, 1889.—CASE 23.—A 27 year old woman had had slight twinges of pain in the middle of the third phalanx of the right fourth finger on its ulnar side for fourteen years. This pain was like a toothache; it was increased by excitement, exposure to cold and changes in temperature, but lessened by heat. Menstruation and two pregnancies had increased the pain, but a third pregnancy did not affect it. All treatment had been unavailing and an exploration a failure. Examination showed a tender slight elevation of the skin, of a bluish color. Under tourniquet, Chisholm removed a round body the size of a pea, soft, lying close to the bone but not adherent to it. Removal cured the condition. Prior to operation he had discussed the case with surgeons of the Massachusetts General Hospital in Boston and was advised that they had seen several similar cases, in all of which a small tumor was found at the seat of the pain causing the pain by pressure on nerve endings. Chisholm suggested that the tumor might represent hypertrophy of a pacinian corpuscle.

Müller, 1901.—In discussing eleven cases of tumor of a finger, Müller described a condition called by him "subungual perithelioma":

CASE 24.—A 44 year old woman had injured the nail bed of the right fourth finger twenty-three years previously. A small blue spot formed under the nail and remained there. There were spontaneous pains and also pains caused by changes

of the weather and by dipping the finger into hot or cold water. Examination showed the nail to be slightly lifted, with a blue spot underneath. A small blue-gray tumor was removed which was not attached to the bone and had a microscopic appearance similar to that in the cases described by Kraske, Kolaczek and Schuh.

*Batigne and Gaudy, 1901.*—These authors described two cases of "fibromatous angioma of the finger":

CASE 25.—A 45 year old man had a small tumor in the middle phalanx of the left fifth finger for six months. It was bluish. The skin was neither adherent to it nor affected. The tumor was removed with ease. It was soft. Rapid healing and complete cure ensued.

CASE 26.—A 25 year old woman had had an enlargement of the palmar surface of the first phalanx of the right fourth finger for five years. There had been a slow steady increase in size. There was slight discomfort on motion of the finger. A tumor was removed with resultant cure.

*Lempert, 1905.* — Discussing subungual angiosarcoma, Lempert includes Kolaczek's and Kraske's cases with the following:

CASE 27.—A 52 year old woman had had pain under the left third finger-nail for ten years. These pains increased. Every motion of the finger hurt. No trauma was reported. Examination showed the nail to be slightly lifted, with a feeling of slight fluctuation beneath it. There was no discoloration. An x-ray photograph showed slight atrophy of the distal phalanx. At operation a tumor the size of a cherry stone, encapsulated and gray-red was removed, with resultant cure. The same pathologic observations were made as in Kolaczek's case.

*Heller, 1927.*—Heller discussed subungual tumors, mentioning the cases of glomal tumor described by Masson, in which classification he included one of Kraske's cases. Under the term "angiosarcoma" he included Kolaczek's case, Lempert's case and Kraske's other case, with one reported by König in which there were multiple tumors of the toes with metastases. (The case observed by König is in our opinion not one of glomal tumor.) He calls the condition in Müller's case "perithelioma" and that in Schuh's "colloid sarcoma."

*Carstensen, 1927.*—Writing on subungual tumors, Carstensen discussed subungual angiosarcoma without being aware of Masson's glomal tumor. She classed her case with Kraske's and Kolaczek's and called them all instances of "perivascular endothelioma."

CASE 28.—A 27 year old woman had had increasing pains in the tip of the right fourth finger for twelve years. These were increased by cold and relieved by heat. Examination showed a bluish red spot under the nail, and the latter was somewhat raised. Removal of the tumor produced complete cure.

*Grieg, 1928.*—Besides describing two proved cases of glomal tumor, Grieg offers one which was not proved pathologically:

CASE 29.—A 70 year old man had a tumor slightly larger than a pea in the right thigh which was tender and sensitive to changes of temperature. No history of injury was obtained, and no treatment was given.

*Hopf, 1930.*—Besides reporting several proved cases, Hopf described another case as follows:

CASE 30.—A 65 year old man had had an injury to his left leg forty-eight years ago. A tumor formed, the size of a hazelnut, which was painful for a few months. The pathologic report was that it was not a typical glomal tumor, and Hopf thought that it might be a "transitional type" of glomal tumor.

*Eisenklam, 1931.*—Discussing subungual tumors, Eisenklam divided them into benign, transitional and malignant groups. Without mentioning glomal tumor, he placed tumors with clinical histories similar to those of glomal tumors in both his transitional and malignant groups. Those with a pathologic diagnosis of sarcoma or carcinoma he placed in the malignant group despite the fact that, as he admits, they are frequently very similar to those in the transitional group.

CASE 31.—A 65 year old man had the nail of his right big toe lifted by a tumor the size of a pea, diagnosed myxoma.

CASE 32.—A 50 year old man had had an injury to his middle finger one year earlier. A blue spot was evident under the nail, and the latter was slightly raised. A tumor was removed from the subungual region, and basal cell carcinoma was diagnosed. There were no metastases, and the patient was fully recovered six months later.

CASE 33.—A 51 year old man had had an injury six months previously. The finger-nail was tender, and there was a blue spot under it. The nail was slightly lifted. Despite the diagnosis of round cell sarcoma, Eisenklam placed this case among those of the transitional group.

#### DIFFERENTIAL DIAGNOSIS OF GLOMAL TUMOR

Although a positive diagnosis can be made only by microscopic section, the clinical course and symptoms of a glomal tumor are so characteristic that, as a rule, a reasonably certain clinical diagnosis should be made with ease. Only one tumor, the subungual melanoblastoma, may cause difficulty in differentiating a glomal tumor.

If the glomal tumor is not situated beneath the nail, it must be differentiated from the smaller tumors of the skin and subdermal tissues. This is easy with respect to warts, nevi, lipomas, fibromas and small sebaceous cysts. Only with respect to the single small superficial neuroma is there room for doubt. As a rule, however, a neuroma in this situation is multiple, not single, and occurs along the course of the cutaneous nerves.

If the glomal tumor is subungual, it must be distinguished from the following benign growths:

*Subungual Exostosis.*—This should be bony hard, demonstrable by x-ray photograph and not productive of either lancinating pains or a bluish subungual discoloration. It also occurs more commonly in children and young adults.

*Subungual Clavus, or Corn.*—This benign tumor may be painful; it occurs at any age of life, and until it grows large enough to protrude beyond the nail it cannot be properly diagnosed. However, it does not cause the bluish discoloration or the excruciating pain.

*Subungual Papilloma.*—This entity is uncommon. Eisenklam mentioned a 20 year old woman who had a painful warty growth under the nail of the left big toe, which was proved to be a papilloma. Unless this grows large enough to be seen or to elevate the nail markedly,

a differential diagnosis cannot be made except by the absence of the bluish discoloration and the sharp pain.

*Subungual Fibroma.*—This benign tumor, as reported by Polland and Dubreuilh, occurs on various fingers and toes, distorting them and the involved nails. Eisenklam, however, reported a case in a 26 year old woman, in which an ulcerating tumor pushed off the nail of the big toe and was proved to be fibroma. Again one notes absence of marked pain and bluish discoloration besides presence of a large neoplasm and multiple tumors.

*Subungual Enchondroma.*—In two cases of multiple enchondroma, as reported by Heller, there were also subungual tumors, but the multiplicity of the tumor provided an easy means of differential diagnosis.

*Subungual Angiokeratoma.*—Under this heading, Schaumann described a tumor under the nail of the right index finger which had started two and a half years previously. There was a red spot under the nail. The tumor grew until it extended beyond the nail, when a biopsy was performed and the diagnosis made. It was treated and cured by radiation. Thus this rare tumor differentiates itself by its growth and radiosensitivity.

*Boeck's Sarcoid.*—Haberman presented two cases of subungual Boeck's sarcoid in conjunction with lesions on other parts of the body. The tumor is an ovoid, hard, paronychia-like lump with a blue-red color and causes marked damage to the growth of the nail. The characteristic appearance of Boeck's sarcoid on the skin when viewed through a glass slide pressed on it is duplicated by the appearance as seen through the nail.

*Sutton's Tumors.*—Sutton reported two cases of tumor at the base of the nail, the definite diagnosis of which he was unable to make. In one case the growth was excised and cure followed; in the other it disappeared on irradiation.

*Melanoblastoma.*—Of the malignant neoplasms, the most important, both numerically and because of the difficulty of differential diagnosis, is the melanoblastoma. Melanoblastoma is the most common malignant subungual tumor, commencing in the majority of the cases very benignly following a slight injury or infection of the subungual tissue. After a period of from months to five years, ulceration of the subungual tissue occurs with either spontaneous or operative removal of the nail. The wound does not heal, and finally pigmented dots are noted. The growth of the tumor has been slow, and usually by the time a diagnosis is definitely made, metastases have already occurred, so that the prognosis is hopeless. Only three exceptions are reported in which early diagnosis and prompt amputation of the affected digit may have prevented metastases. Prior to the appearance of ulceration and deposits

of black pigment, the tumor frequently is benign looking. Commonly the bluish-black spot seen under the nail resembles somewhat that seen with the glomal tumor. Microscopically there is not the least resemblance between the two tumors.

*Sarcoma.*—True malignant sarcomas with metastases do occur but very infrequently, if the benign tumors previously incorrectly called "sarcoma" are excluded. Heller cited seven cases of sarcoma with metastases from the literature. Eisenklam reported a case of "round cell sarcoma" in which a 14 year old girl had a painful swelling of the left big toe. This ulcerated and discharged material through a fistulous opening. A pea-sized blue-red tumor was removed from under the nail. Wurnbrund reported a case of chondrosarcoma.

*Carcinoma.*—Under this heading a case was reported, by Pinheiro-Chagas, of a 60 year old laborer whose big toe had been injured eighteen years earlier. A tumor developed in the nail matrix of the toe; it was proved pathologically to be an epithelioma. Heidingsfeld wrote of a 60 year old man who had had ulcerations at the base of the right thumb-nail for nine years. This area was very tender and the trouble caused incapacitating pains. All treatments had been unsuccessful till Heidingsfeld used radium, with which he obtained complete cure. Under this heading we are including a case reported by Suter of a 39 year old man who had cut his left thumb eight years earlier. Following this the nail began to curl under and grew into the pulp. Later the thumb became swollen and was extremely painful. The swelling and pain were exaggerated when the thumb was crushed in a second accident. The patient entered the hospital with a tumor the size of a hazelnut, for which part of the thumb was amputated. Pathologic examination revealed the tip of the distal phalanx eroded and invaded by tumor cells. Apparently complete cure resulted.

#### SUMMARY

Three cases of glomal tumor, the first to be recorded in the American literature, are added to the list of twenty-six cases previously reported.<sup>1</sup> This benign tumor, first authentically described by Masson in 1924, develops from a structure normally present in the skin and known as the glomus. It is probably identical with the "painful subcutaneous nodule" reported by Wood in 1812, referred to by Paget in 1853 and

---

1. Since this article was written, eleven additional cases of glomal tumor have been reported: one by Drs. Mason and Weil (Mason, M. L., and Weil, A.: Tumor of a Subcutaneous Glomus; *Tumeur Glomique*; *Tumeur du Glomus Neuro-Myo-Arterial*; *Subcutaneous Painful Tubercle*; *Angio-Myo-Neurome*; *Subcutaneous Global Tumor*, *Surg. Gynec. & Obst.* **58**:807 [May] 1934) and ten cases reported by Dr. Adair (Adair, F. E.: *Glomus Tumor: Clinical Study with Report of 10 Cases*, *Am. J. Surg.* **25**:1 [July] 1934).

described by other authors as "colloid sarcoma" (Heller), "painful subcutaneous fibroma" (Tillaux), "angiosarcoma" (Kolaczek), "painful subcutaneous angioma" (Monod) and "subungual perithelioma" (Müller). Thirty-three instances have been collected by us and reported as "probable but unproved cases of glomal tumor."

The glomal tumor has a characteristic microscopic appearance and a typical clinical course. It is small, usually not more than  $\frac{1}{2}$  inch (1.27 cm.) in diameter, of slow growth and long duration. It may be situated in any part of the body, but the favorite site is beneath the nail. There it gives rise to pain of varying intensity and radiation. In the severe cases the pain is agonizing, almost paroxysmal, and radiates upward to the shoulder, even to the heart. When the tumor is not subungual, the pain is usually much less severe. Changes of temperature, particularly cold, increase the severity of the pain. Invariably, the tumor is sensitive to pressure. In some cases it is associated with neurologic or vascular changes such as hyperesthesia and increase in the temperature of the skin. In two cases there was slight atrophy of the entire arm, and in one Horner's syndrome. Examination reveals a pea-sized tender tumor, which, when subungual, has almost always a peculiar bluish tinge showing through the translucent nail. The x-ray picture of the growth in this situation may show a minute crater-like depression of the dorsal cortex of the terminal phalanx.

The only effective treatment is excision by knife or by endothermy. If the tumor is subungual, exposure is secured by removal of a portion of the nail, which in our own case and in many others, regenerated normally. The tumor may be encapsulated as in the majority of cases, or diffuse as in our first patient. No metastases or recurrences after excision have been reported. Invariably pain has disappeared after removal of the tumor.

Glomal tumor is easily differentiated from most of the cutaneous neoplasms. Only two of the latter may cause difficulty: first, the unusual single small neuroma, superficially located; second, the subungual melanoblastoma. This very malignant tumor at one phase of its development is characterized by a bluish-black spot beneath the nail which might be mistaken for a glomus. Operation and microscopic section will at once make the differential diagnosis possible.

#### BIBLIOGRAPHY

- Barré, J. A.: *Certaines symptomatologies de la périphérie des membres*, Paris méd. 2:311 (Oct. 7) 1922.  
 —and Masson: *Tumeurs du glomus neuro-myo-artériel des extrémités*, Bull. Soc. franç. de dermat. et syph. 31:148, 1924.  
 Batigne and Gaudy: *Angiome fibro-myomateux du doigt*, Bull. et mém. Soc. anat. de Paris 76:687, 1901.



- Bonnet, M. P.: Tumeur sous-unguéale douloureuse (glomus), *Lyon chir.* **24**:748, 1927.
- Carstensen, L.: Ueber subunguale Tumoren, *Arch. f. klin. Chir.* **144**:409, 1927.
- Chandelux, A.: Recherches sur les tubercules sous-cutanés douloureux, *Arch. de physiol. norm. et path.* **9**:639, 1882.
- Chisholm, M.: Painful Fibroma at the End of the Ring Finger, *Maritime M. News, Halifax* **1**:57, 1889.
- Costa, A. J.: Tumor del glomus neuromioarterial del dedo indice izquierdo, *Bol. y trab. de la Soc. de cir. de Buenos Aires* **16**:151, 1932.
- Crampton, P.: Painful Subcutaneous Tubercle, *Dublin J. M. Sc.* **15**:470, 1853.
- Dubreuilh: Fibromes multiples du lit de l'ongle, *Bull. Soc. franç. de dermat. et syph.* **30**:208, 1923.
- Dupont, A.: Aspects atypiques des tumeurs glomiques, *Rev. belge sc. méd.* **3**:624, 1931.
- Eisenklam, D.: Ueber subunguale Tumoren, *Wien. klin. Wchnschr.* **44**:1192, 1931.
- Fernandez and Mousserat: Nodules dolorosos de la oreja, *Semana méd.* **38**:1693, 1931.
- Greig, D. M.: Subcutaneous Glomar Tumors, *Edinburgh M. J.* **35**:565, 1928.
- Haberman, R.: Boecksche Sarkoide an den Nagelphalangen, *Dermat. Wchnschr.* **87**:1259, 1928.
- Heidingsfeld: Epithelioma Radicis Unguis, *Lancet-Clinic* **113**:583, 1915.
- Heller, J.: Krankheiten der Nägel, in Jadassohn, J.: *Handbuch der Haut und Geschlechtskrankheiten*, Berlin, Julius Springer, 1927, vol. 13, pt. 2, p. 158.
- Hertzer, A. E.: Melanoblastoma of Nail-Bed (Melanotic Whitlow), *Arch. Dermat. & Syph.* **6**:701 (Dec.) 1922.
- Hopf, M.: Ueber Tumoren des neuromyoarteriellen Glomus, *Frankfurt Ztschr. f. Path.* **40**:387, 1930.
- Ianichewski, A., and Lebel, M.: Sympathalgie due à une tumeur glomique, *Presse méd.* **36**:116 (Jan. 28) 1928.
- Jones, T. B.: Melanoma of Nail-Bed, *Ann. Surg.* **80**:839, 1924.
- Kolaczek, J.: Ueber das Angiosarkom, *Deutsche Ztschr. f. Chir.* **9**:176, 1878.
- Kraske, P.: Ueber subunguale Geschwülste, *München. med. Wchnschr.* **34**:889, 1887.
- Labbé and Legros: Trois cas de neuromes, *J. de l'anat. et de la physiol.* **7**:171, 1870-1871.
- Lediard, H. A.: Melanotic Sarcoma from Edge of Nail, *Tr. Path. Soc., London* **39**:307, 1888.
- Lempert, L.: Ueber subunguale Angiosarkome, *Inaug. Dissert., Charlottenburg, J. Zalachowski*, 1905.
- Lortat-Jacob and Brosse: Tumeur sous-unguéale violacée, *Bull. Soc. franç. de dermat. et syph.* **35**:305, 1928.
- Martin and Dechaume: Les tumeurs glomiques, *Ann. d'anat. path.* **2**:239, 1925.
- Masson, P.: Glomus neuro-myo-artériel des régions tactiles et ses tumeurs, *Lyon chir.* **21**:257, 1924.
- and Gery: Les tumeurs glomiques sous-cutanées en dehors des doigts (angio-neuromyomes artériels), *Ann. d'anat. path.* **4**:153, 1927.
- Monod, C.: Angiomes douloureux, *Bull. et mém. Soc. de chir. de Paris* **5**:652, 1879.
- Montgomery, D. W., and Culver, G. D.: Verruca of the Nail Fold, *Arch. Dermat. & Syph.* **10**:425 (Oct.) 1924.
- Müller, R. F.: Zur Kenntnis der Fingergeschwülste, *Arch. f. klin. Chir.* **63**:348, 1901.

- Nicod, J. L.: Le glomus neuro-myo-artériel sous-cutané, *Schweiz. med. Wchnschr.* **57**:1157, 1927.
- Paget, James: Painful Subcutaneous Tumors, *Lectures on Surgical Pathology*, London, Longman [and others], 1853, vol. 2, p. 120.
- Paulian: Stefan-Popescu and Marinesco-Slatina: Tumeur glomique sous-unguéale suivie d'hémihyperthermie et guérison complète après l'ablation chirurgicale, *Ann. d'anat. path.* **10**:271, 1933.
- Picard, H.: Neuromyoarterielle Glomustumoren, *Zentralbl. f. Chir.* **58**:2133, 1931.
- Pinheiro-Chagas: Carcinoma in Nail Matrix of Big Toe, *Brazil-med.* **35**:233, 1921.
- Polland, R.: Fibromatosis subungualis, *Dermat. Ztschr.* **23**:542, 1916.
- Probststein, J. G., and Brooks, B.: Subungual Exostosis, *J. Missouri M. A.* **22**:211 (June) 1925.
- Prodanoff, A.: Sur la localisation des tumeurs glomiques (angio-neuromyome de P. Masson), *Ann. d'anat. path.* **4**:147, 1927.
- Schaumann, J.: Cas d'angiokératome sous-unguéale, *Acta dermat.-venereol.* **3**:428, 1922.
- Schuh: Einige seltene Neubildungen, *Oesterr. Ztschr. f. prakt. Heilkunde* **8**:74, 1862.
- Specht, K.: Ueber das primäre subunguale maligne Melanoblastom, *Deutsche Ztschr. f. Chir.* **202**:390, 1927.
- Suter, F. A.: Zur Casuistik der Fingertumoren, *Arch. f. klin. Chir.* **75**:624, 1905.
- Sutton, R. L.: Nail Tumor of Unusual Type, *Arch. Dermat. & Syph.* **6**:351 (Sept.) 1922.
- Tillaux: Fibrome sous-cutané douloureux, *Gaz. d. hôp.* **43**:178, 1870.
- Wood, William: Painful Subcutaneous Tubercle, *Edinburgh M. J.* **8**:283, 1812.
- Wurmbrund, G.: Kasuistik der subungualen Zehensarkome, *Deutsche Ztschr. f. Chir.* **107**:445, 1910.

# OTOGENOUS ABSCESS OF THE PARIETAL LOBE

REVIEW OF THE LITERATURE AND REPORT OF SIX CASES

CYRIL B. COURVILLE, M.D.

AND

J. M. NIELSEN, M.D.

LOS ANGELES

Otogenous abscess of the brain is commonly located in the temporal lobe or cerebellum. This dictum has proved to be true so often that the exceptions to it—cases of abscess in another cerebral lobe—have been almost entirely forgotten or ignored. The more critical reviews concerned with intracranial complications of otitis media refer to individual and often isolated cases of abscess in the frontal, parietal or occipital lobe. Those in the frontal lobe, perhaps because of their greater incidence in this “remote” group, have been given most attention. That these more distant abscesses are not as uncommon as they first appear to be is indicated by their frequency in any large series of cases of otitic abscesses verified at autopsy. This incidence is not absolute, for an increasing percentage of patients with abscess in the temporal lobe or cerebellum are cured by surgical drainage, while abscess elsewhere has been almost uniformly fatal. The percentage is still sufficiently high to warrant a more careful study of these cases than they have received.

No attempt has previously been made to study cases of otogenous abscess in the parietal lobe. Many monographs concerned with abscess of the brain do not even take cognizance of the possibility of such an occurrence. Our experience with 6 examples of parietal localization in a group of 63 cases of otogenous abscess of the brain has led us to believe that more attention should be given to it clinically. In this study an attempt has been made to discover its pathogenesis and characteristic pathology and to note particularly its symptomatology so that the presence of the abscess may be detected more often during life.

## REVIEW OF THE LITERATURE

While otogenous abscess of the parietal lobe is without doubt more common than is generally suspected, a review of the literature fails to disclose many examples. A few are reported under significant titles,

---

From the Departments of Neurology of the College of Medical Evangelists and the University of Southern California, and the Ramón Cajal Laboratory of Neuropathology, Los Angeles County General Hospital.

but most of them are included in reviews of the subject of otogenous abscess in general or incidentally in other connections.<sup>1</sup>

1. In this review two sources of error in reporting instances of otitic parietal abscess have come to light. The first, which makes a complete collection of cases well-nigh impossible, is the mistaking of abscess of the parietal lobe for that of the temporal lobe for want of a critical interpretation of the exact site of puncture of the brain in the patients operated on or for want of postmortem study. The second type of error, that of designating as an abscess of the parietal lobe one situated in the frontal or temporal lobe, is discovered when an attempt is made to study the often meager details in the articles listed under this title. A brief review of cases which are reported or cited as cases of abscess of the parietal lobe but which we are inclined to classify otherwise is in order.

In the oft cited case of Hegener (*Demonstration zur Lehre vom Hirnabszess, Verhandl. d. deutsch. otol. Gesellsch.* 16:201, 1907), for example, the lesion proved to be primarily an abscess of the centrum beneath the lower portion of the right precentral convolution which also extended caudally to lie partially beneath the postcentral gyrus. The abscess in another case cited in this article (from Manasse's clinic) evidently lay beneath the left superior temporal convolution. In both instances the abscess was associated with thrombosis of the inferior anastomotic vein and was probably secondary to it. While these cases shed considerable light on the pathogenesis of distant otogenous abscess, they cannot be accepted as examples of parietal localization.

The case of Piffi and Pötzl (*Ein otogener parietaler Hirnabszess [Rückbildung einer parietalen pseudosensorischen Aphasie], Arch. f. Ohren-, Nasen- u. Kehlkopfh.* 112:93, 1925) is evidently not one of parietal abscess. Their illustration (fig. 1) shows that the region through which the abscess was drained was temporo-occipital. It is likely that the sensory aphasia was due to pressure on the "centers" from below. The patient recovered.

Although Harms' case (*Ein geheilter Fall von multipler Hirnabszess-Bildung nach akuter Mittelohreiterung, Ztschr. f. Ohrenh.* 72:118, 1915) was accepted by his contemporaries as an example of otitic parietal abscess, we are inclined to exclude it also. What was thought to be an abscess in the left temporal lobe was first tapped through the mastoid wound and later through another opening in the temporal region. No cultures of the material recovered from the brain or from the mastoid were made. At a third session a puncture made through the temporal opening and directed upward and backward, supposedly into the inferior parietal convolution, resulted in the recovery of about 5 cc. of a clear serous, yellowish fluid. *Staphylococcus albus* was cultured from this fluid. Even if the fluid was recovered from the parietal lobe, which was very doubtful, it was not characteristic of the contents of a recent abscess. It was more likely fluid collected outside the capsule of the abscess previously tapped.

The case of Ferretti (*Su un interessante caso di ascesso cerebrale di origine otitica a decorso eccezionalmente lungo, Arch. ital. di otol.* 38:135, 1927) has also been cited recently as an example of parietal abscess. At autopsy there was found an adhesion of the dura mater to the brain over the right inferior parietal lobule and adjoining portion of the temporal lobe, the residuum of an old subdural infection. Incision of the brain revealed an encapsulated abscess about the size of a walnut which had ruptured into the floor of the inferior horn of the lateral ventricle. While the author was not entirely clear as to the exact location of the abscess, there is nothing in the description to lead one to believe that it was situated within the parietal lobe.

According to Gowers,<sup>2</sup> the parietal lobe is the least common site of otitic abscess of the brain. As late as 1918, Blau<sup>3</sup> found only 2 examples of abscess in a collected series of 352 instances of otogenic abscess of the brain. In a series of 14,534 autopsies, Evans<sup>4</sup> found 194 instances of abscess of the brain, of which 109 (56 per cent) were stated to be consequent to otitis media and mastoiditis. Of this number, 62 abscesses were cerebral and 40 cerebellar, while in 7 instances an abscess was present in both the cerebrum and the cerebellum. Of the 62 cases of cerebral abscess, the temporal lobe was the seat of infection in 56. In 3 cases the abscess was located in the occipital lobe, in 2 in the parietal lobe and in 1 in the frontal lobe.

The first recorded cases that we have been able to discover were reported by Pitt<sup>5</sup> as instances of abscess of the centrum ovale. In 1 case the abscess was apparently secondary to thrombosis of a superficial vein (from the sylvian fissure to the dura), possibly the vena anastomotica superior. In the second case 3 abscesses were found in the hemisphere opposite the infected ear. Moreover, in the lateral sinus adjacent to this ear there was an old thrombus which extended into the posterior half of the superior longitudinal sinus. In both these cases the abscess was discovered at autopsy. In a study of abscess of the brain in infants, Holt<sup>6</sup> reported 2 examples of otitic abscess of the parietal lobe. An infant, aged 6 weeks, died shortly after the onset of bilateral otitis media. A large abscess was found at autopsy; it filled the entire left parietal lobe and extended to the ependyma of the lateral ventricle. In the second case an infant, aged 3 months, had generalized convulsions and died shortly after. A large abscess was found in the right parietal lobe, and there was also an elongated abscess above the corpus callosum on the left side which had ruptured into the lateral ventricle. Pus was found in the left ear. Shortly after the appearance of Holt's study, Westphal<sup>7</sup> described a case of abscess of the left parietal lobe in a woman, aged 34, which was thought to be secondary

2. Gowers, W. F.: *A Manual of Diseases of the Nervous System*, ed. 2, Philadelphia, P. Blakiston's Son & Co., 1898, vol. 2, p. 475.

3. Blau, L.: *Zur Lehre von den otogenen intrakraniellen Erkrankungen. Gehirnabszess-Sinusthrombose-Meningitis*, Beitr. z. Anat., Physiol., Path. u. Therap. d. Ohres **10**:86, 1918.

4. Evans, William: *The Pathology and Aetiology of Brain Abscess*, *Lancet* **1**:1231 (June 6); 1289 (June 13) 1931. Dr. Evans permitted us to use these data in his 2 instances of parietal abscess (table).

5. Pitt, G. N.: *Goulstonian Lectures on Some Cerebral Lesions*, *Brit. M. J.* **1**:643 (March 22) 1890.

6. Holt, L. E.: *A Report of Five Cases of Abscess of the Brain in Infants, Together with a Summary of Twenty-Seven Collected Cases*, *Arch. Pediat.* **15**: 81 (Feb.) 1898.

7. Westphal, A.: *Ueber Gehirnabscesse*, *Arch. f. Psychiat.* **33**:206, 1900.

*Data on Collected Cases of Oligonous Abscess of the Parietal Lobe*

Author	Case	Age	Sex	Otitis Media	Hemisphere	Type of Abscess	Associated Lesions
Pitt.....	1	?	?	?	?	?	Thrombosis of the superolateral cerebral vein (Tro- und ?)
	2	5 years	F	Acute	?	Multiple abscesses of the centrum of the opposite hemisphere	Thrombosis of the lateral sinus and the superior longitudinal sinus
Holt.....	1	6 weeks	F	Acute	Left	Acute, thin-walled	Local meningitis
	2	3 months	F	Acute	Right and left	Not stated	Not stated
Westphal.....	..	3½ years	F	Acute	Left	Encapsulated	Not stated
Harris.....	..	30 years	F	Chronic	Left	"Recent"	Communicated with an abscess of the left temporal lobe
Lubliner.....	..	16 years	F	Acute	Left	Not stated	Subdural abscess; abscess of the left temporal lobe
Uehermann.....	..	?	?	?	?	?	Thrombosis of the lateral sinus
Urbansehtsch.....	..	35 years	M	Chronic	Left	Multiple small abscesses	Thrombosis of the right lateral sinus; abscess of the right frontal lobe
Coates and Case.....	..	37 years	M	Chronic	Left	Not stated	Two abscesses (left frontal lobe and left temporal lobe)
Bryan.....	..	23 years	M	Chronic	Left	Not stated	Subdural abscess; abscess of the left temporal lobe; meningitis
Vibede.....	..	14 months	M	Acute	Right	Evidently recent	Thrombosis of the right lateral and superior longi- tudinal sinuses and the right superior cerebral veins
Evans.....	1	6 months	F	Acute	Left	Large, thin-walled involving the adjacent lobes	Meningitis; internal hydrocephalus; thrombosis of the right inferior cerebral vein, right middle cerebral vein and right lateral sinus
Ghsburg.....	2	15 years	M	Acute	Left	Fully large, thin- walled	Thrombosis of the left lateral sinus; extensive softening of the brain
	..	?	?	?	Left (?)	Not stated	Thrombosis of the right lateral sinus (?); subdural abscess (?)
Fraser.....	..	15 years	M	Chronic	Right	Not stated	Basilar meningitis; mural thrombus in the left lateral sinus (surgical diagnosis)
Collins.....	..	?	?	Chronic	Right	Not stated	Abscess also found in the left frontal and tem- poral lobes
Faunce and Shambaugh..	..	10 years	M	Acute	Right	Encapsulated	Thrombosis of the right lateral sinus, right superior petrosal sinus, right inferior cerebral vein and right inferior anastomatic vein; abscess of the right occip- ital lobe
Courville and Nielsen.....	1	45 years	M	Chronic	Left	Large circumserbed	Adhesion of the tentorium, dura and brain on the left
	2	10 months	M	Acute	Left	Early	Epidemic brain
	3	37 years	M	Chronic	Right	Large, recent	Thrombosis of the right lateral sinus; subdural abscess on the right side
	4	32 years	M	Acute ?	Right	Large, poorly encapsulated	Meningitis
	5	2½ years	F	Acute	Left	Small, encapsulated (surgical intervention)	Recovery; no known complications
	6	8 years	F	Acute	Right	Large, thin-walled	Softening of the surrounding brain

to a pelvic infection. However, during life bilateral otitis media was found to be present. The onset of the cerebral lesion was manifested two and one-half months before death by epileptiform seizures followed by aphasia and right hemiplegia. At autopsy an encapsulated abscess was found.

The case described by Harris<sup>8</sup> was unique and typical of a group of otogenous abscesses of the parietal lobe secondary to those in other parts of the brain. A recurrent attack of otitis media in an adult, aged 30, resulted in generalized convulsions and death. At autopsy there was found an adjacent abscess in the temporal lobe with a "stalk" leading to an erosion of the tegmen. This abscess was connected by a fistulous tract with another in the parietal lobe. Lubliner<sup>9</sup> reported a similar case, an abscess in the parietal lobe being considered secondary to one in the temporal lobe. A subdural abscess had previously been drained at the time of operation.<sup>10</sup> The case reported by Coates and Case<sup>11</sup> also belongs to this group. The abscess which they found in the parietal lobe was evidently an extension from one of two abscesses in the frontal lobe of the left side. A discolored, softened area in the white substance of the left temporal lobe indicated a more recent abscess in this situation.

In another interesting group of cases the parietal abscess is associated with thrombosis of the venous channels, particularly of the lateral sinus. As in the previous group, other abscesses may be found in the ipsilateral or even in the contralateral hemisphere. Uchermann<sup>12</sup> described an abscess associated with thrombosis of the lateral sinus of the same side;

---

8. Harris, T. J.: Pathologic Findings of the Intra-Cranial Complications of Middle Ear Disease, *Laryngoscope* **15**:535 (July) 1905.

9. Lubliner: *Monatschr. f. Ohrenh.* **49**:25, 1913.

10. In these two instances the description of the cerebral lesion was too meager to permit one to gain any accurate concept as to the course of the infection as it passed from the temporal to the parietal lobe. In coronal sections of the brain in this region it is found that the two lobes, save in their most caudal portions, are separated by the rather deep sylvian fissure. Infection extending from the temporal to the parietal lobe must either cross this fissure or go by way of the rather narrow external capsule, a most unlikely development. If the fissure is crossed, there will be necessarily a preliminary meningocerebral adhesion uniting the opposed surfaces of the lobes in the fissure. Infection would then pass through this sealed-off area much as it does from the tegmen into the basilar surface to form the original temporal abscess. In these unusual cases, the brain should be given more critical study, for these cases shed a great deal of light on the many unsolved problems of otitic intracranial complications.

11. Coates, G. M., and Case, A. E.: Multiple Brain Abscesses Following Otitis Media, *Ann. Otol., Rhin. & Laryng.* **33**:335 (June) 1924.

12. Uchermann, V.: Otogene Hirnabscesse im Frontallappen und im Parietallappen, *Monatschr. f. Ohrenh.* **49**:561, 1914.

both the abscess and the thrombosis were otitic in origin. In the case reported by Urbantschitsch<sup>13</sup> multiple small abscesses were found in the left parietal lobe, with a larger one in the right frontal lobe. A chronically affected right ear was also complicated by thrombosis of the right lateral sinus. One of the cases of Pitt, already referred to, belongs to this group. In both of Evans' cases<sup>4</sup> there was found a thrombosis of the lateral sinus. In 1 of these the middle and inferior cerebral veins were also occluded. In this case the abscess was situated in the opposite parietal lobe. The recently reported case of Faunce and Shambaugh<sup>14</sup> is of interest in that two abscesses, one in the right inferior parietal region and the other in the parieto-occipital region, were associated with thrombosis of the right lateral and right superior petrosal sinuses and of the cortical veins of the regional dorsolateral surface of the hemisphere. The lesions were secondary to a transitory otitis media.

Thrombosis of the lateral sinus is not always present, however, in cases of multiple abscesses. For example, in Bryan's<sup>15</sup> case one abscess, which had been drained surgically, was situated in the left parietal lobe and a second was found at autopsy in the left temporal lobe. A subdural abscess was also found in the middle fossa on the left side.<sup>15a</sup>

A review of the available literature, therefore, leads one to conclude that, though rare, otogenous abscess of the parietal lobe does occur and that in many instances it has been mistaken, so far as location is concerned, for abscess in the temporal, the frontal or the occipital lobe.

13. Urbantschitsch, E.: Kontralaterale Hirnabscesse, *Monatschr. f. Ohrenh.* 52:50, 1918.

14. Faunce, C. B., and Shambaugh, G. E., Jr.: Abscess of the Brain Following Mild Transitory Otitis Media, *Arch. Otolaryng.* 17:673 (May) 1933.

15. Bryan, J. H.: Abscess of the Brain of Otitic Origin, *Ann. Otol., Rhin. & Laryng.* 37:819 (Sept.) 1928.

15a. In a more recent general survey of the literature on intracranial complications of otitis media, we found three additional references to parietal abscess. Ginsburg (Otogene Hirnabscesse nach den Beobachtungen der oto-laryngologischen Klinik in Dnjepropetrowsk, abstr., *Zentralbl. f. Hals-, Nasen- u. Ohrenh.* 18:236, 1932) found 1 contralateral parietal abscess in 11 cases of otogenous abscess of the brain. The details of the clinical history or autopsy observations were not given. In Vibede's case (Tilfaelde af otogen hjaernabsces, *Hospitaltid.* 67:33, 1924), a parietal abscess on the right side was found at autopsy, evidently due to retrograde extension from the right lateral and the superior longitudinal sinus into the superior cerebral veins, draining the parietal lobe. In Fraser's case (Sigmoid Sinus Thrombosis (L.); Metastatic Parietal Lobe Abscess; Death, *J. Laryng. & Otol.* 48:274 [April] 1933) a right parietal abscess was found at autopsy. During life a mural thrombus was removed surgically from the left lateral sinus. Before death, marked weakness and loss of sensation were noted in the left arm and leg. In discussing Fraser's case, Collins recalled having seen a case of multiple abscess of the brain evidently secondary to chronic otitis media on the right side. One abscess was located in the right parietal lobe, another in the left frontal lobe and still another in the left temporal lobe. These cases are included in the table.



The parietal abscess may be one of two or more in one or both cerebral hemispheres, suggesting a vascular spread of infection. The occurrence of an associated thrombosis of the lateral sinus or of the connecting venous channels indicates that the route of infection is by the venous rather than the arterial route. The essential details of reported cases are included in the accompanying table.

#### REPORT OF CASES

As is so often the case, the history of our experience with otitic parietal abscess began with a diagnostic failure followed promptly by a therapeutic disaster. To be sure, the clinical symptoms were somewhat unusual for an abscess of the temporal lobe, which was originally suspected. The difficulty in establishing the existence of a predisposing infection in the middle ear, however, served to deflect our attention from the conspicuous motor and sensory manifestations. The post-mortem disclosure of a large circumscribed abscess within the parietal centrum served to emphasize the meaning of these symptoms, a lesson which served us in good stead when the next patient came under our observation. In the meantime, a review of a large series of records of postmortem examinations revealed 3 additional cases. A short note on the 3 cases found in the records of the department of pathology precedes the reports on the 2 cases which came to our attention clinically. We also had an opportunity (case 6) to study a specimen brought to the laboratory in which a parietal abscess was found.

*CASE 1.—Chronic left otitis media and mastoiditis in a man. Death following mastoidectomy. Autopsy. A large circumscribed abscess in the left parietal lobe.*

An emaciated Mexican man, aged 45, died on July 25, 1918, following a mastoidectomy. He had been admitted on July 18, 1918, to the Los Angeles County General Hospital, but no further information was available, the clinical record having been destroyed.

At autopsy a recent surgical wound was found in the left mastoid region. On removal of the calvarium the dura was found to be tense and hyperemic. The cerebral cortex was also hyperemic. At the base of the left temporal lobe the brain and dura and in turn the dura and bone of the tegmen tympani were found to be firmly adherent to each other. When the brain was sectioned, a large, well circumscribed abscess filled with thick green pus was found to occupy the centrum of the left parietal lobe. The left temporal bone was carious and honey-combed with abscesses. The causative organism was not identified.

*Comment.*—The emaciation of the patient, the complete delineation of the abscess and the firm local adhesions speak for a chronic infection. It was of interest to find the classic prerequisites of a temporal abscess—adhesion of the dura to the bone and to the brain—but the development of a parietal infection. A complete clinical history would have been most desirable in a study of this case.

CASE 2.—*Death of an infant with signs of bronchopneumonia. Autopsy. Bilateral otitis media. Softening of the cerebral cortex in the left parietal region which proved to be infarction with early formation of abscess.*

A Mexican boy, aged 10 months, was admitted to the Los Angeles County General Hospital in a moribund state on Nov. 19, 1930, and died within three hours. No history was obtained at the time other than that the child had been acutely ill with a fever for three days. The child was cyanotic, dyspneic and lethargic.

At autopsy the brain was found to be edematous. The meninges showed no gross change. The cerebral cortex was found to be softened in the left parietal region. Sections taken from this area for microscopic examination revealed an extensive infarction of the cortex and underlying white matter. With the exception of the nuclei of the neuroglia the cellular elements were not demonstrated by routine staining methods. In several situations within this infarcted area there were accumulations of leukocytes. Polymorphonuclear cells predominated in the center of each collection of cells, while lymphocytes formed an irregular peripheral zone. They were especially conspicuous in the form of "cuffs" in the spaces about the regional blood vessels. A mucopurulent exudate was found in each middle ear, being most abundant in the right ear. Bilateral bronchopneumonia was also present. A pneumococcus was the infecting organism.

*Comment.*—The clinical record of this case is unfortunately incomplete. Every effort has been made, even after an interval of years, to secure a more detailed history of the child's illness, but without success. It would have been particularly enlightening to know whether or not convulsions, particularly the jacksonian variety, occurred.

CASE 3.—*Recurrent right otitis media with mastoiditis. Necrosis of the tegmen antri. Surgical drainage of the subdural abscess through the temporal route. Death after five days. Autopsy disclosed a right parietal abscess and thrombosis of the right lateral sinus.*

A Mexican man, aged 37, was admitted to the Los Angeles County General Hospital on March 23, 1934, with a history of recurrent attacks of otitis media on the right for many years. He complained of headaches and pain in the right ear and appeared extremely ill. At times he was definitely irrational. There was definite tenderness on pressure over the right mastoid. The temperature was somewhat subnormal, and the pulse was found to be slowed (from 64 to 68) on several occasions. Roentgenograms revealed an increased density of both mastoids (sclerosis) with some possible rarefaction on the right in the region of the genu of the lateral sinus. A white blood cell count revealed 20,600 leukocytes per cubic millimeter, 90 per cent of which were polymorphonuclears.

On later examination a definite weakness of the left arm, leg and left lower region of the face was found. The eyegrounds were reported to be normal.

Mastoidectomy on the right was performed on March 25 by Dr. Isaac Jones, who found necrosis of the bone forming the tegmen antri and the posterior wall of the external auditory canal. Granulation tissue covered the dura above the tegmen. It seemed evident that a cerebral abscess existed, and a trephine opening was made in the right temporal region by Dr. Carl W. Rand. On opening the dura, a large amount of greenish-yellow pus welled up into the wound. Several drains were placed in the subdural space and the wound closed. Culture of the pus from the mastoid and subdural space revealed that the offending organism was a pneumococcus.

The patient did poorly following the operation. The next morning he had several generalized convulsions and was noisy and talkative. He was unable to swallow. The temperature remained about normal, and the pulse rate varied between 70 and 112 per minute. A Cheyne-Stokes type of respiration developed, and the patient died on March 30, after an abrupt rise of temperature to 106 F.

At autopsy the right lateral sinus was found to be completely thrombosed, as were the venous channels in the parietal region. This surface of the hemisphere was covered with thick green pus which also adhered to the inner surface of the dura. There was a fistulous opening in the dura over the tegmen antri which extended into the operative excavation in the mastoid bone.

In the centrum of the right parietal lobe there was a large, softened, necrotic area which had a dark green color; it was evidently a very early abscess. This area did not communicate with the ventricular system. There was no gross evidence of involvement of the temporal lobe.

*Comment.*—This case presents several points of interest. The presence of thrombosis of the lateral sinus suggests a possible etiologic relationship between this lesion and the abscess, especially since the venous channels in the parietal region were also occluded. It is also possible but not likely that the parietal abscess was secondary to the subdural abscess which covered the dorsolateral surface of this hemisphere. The abscess was obviously a very recent one.

*CASE 4.*—*Transient otitis media on the right in an adult. Development of left hemiplegia, headache and stupor. Surgical exploration with tapping of the abscess high in the centrum of the right cerebral hemisphere. Death from septic meningitis. Autopsy.*<sup>16</sup>

A white man, aged 32, was admitted to the neurologic service of the Los Angeles County General Hospital on Jan. 1, 1930, with the complaint of headache for five or six weeks and weakness of the left side for four weeks. The patient's wife stated that the patient had had a severe cold in the head six weeks before, its appearance being followed shortly by a purulent discharge from the right ear and generalized throbbing headaches. The minor discharge ceased spontaneously after two or three weeks. A week after the onset of otitis media, the patient noticed paresthesia and numbness beginning in the left leg and extending upward to the left arm. Following these sensory manifestations the affected members felt "dead." Progressive left hemiplegia then developed, associated with increasingly severe headaches. The patient described several fainting spells; when we questioned his wife we learned that these were attacks of generalized convulsions.

Examination on admission revealed a somewhat inattentive and at times drowsy man who presented conjugate deviation of the head and eyes toward the right and well marked spastic left hemiplegia and hemihypesthesia. The pupils were unequal, the right being smaller than the left. Both reacted somewhat poorly to light. The nasal half of the right optic disk was blurred. There was slight rigidity of the neck, but the Kernig sign was not elicited. The deep reflexes were exaggerated on the left and associated with a bilateral Babinski sign, which was more marked on the left. The cremasteric reflex was absent on the left.

Lumbar puncture revealed a clear spinal fluid under increased pressure, but otherwise normal. The white blood cell count was 14,250 cells per cubic milli-

16. This case has been reported in brief by Meyers (Conjugate Deviation of the Head and Eyes, Arch. Otolaryng. 13:683 [May] 1931) in another connection.

meter, of which 77 per cent were polymorphonuclears. Roentgenograms of the skull revealed an increase in density in the mastoid portion of the right temporal bone.

Under ether anesthesia, exploration of the brain was made on Jan. 7, 1930, by Dr. George H. Patterson. A trephine opening was made over the right ear, somewhat higher than usual for an exploration of the temporal lobe. Repeated punctures in the temporal lobe failed to reveal an abscess. An abscess at a depth of 5 cm. was tapped by an oblique puncture upward and slightly backward toward the parietal lobe. An abundance of greenish-yellow pus was recovered, from which a pneumococcus was cultured.

The patient promptly recovered from his stuporous state and had temporary relief from his headaches. His improvement was short-lived, however, for a gradually rising temperature and symptoms of meningeal irritation soon made their appearance. A lumbar puncture revealed a cloudy spinal fluid, and pneumococci were found on smear and culture. He died on January 14, 1930.

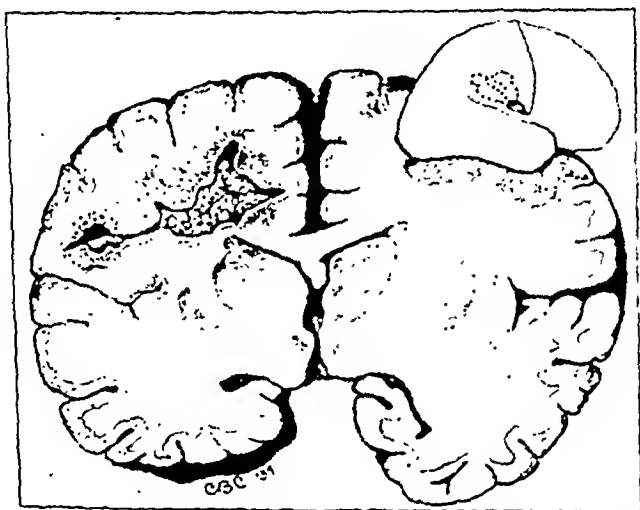


Fig. 1 (case 4).—Drawing of a coronal section of the brain, showing the abscess in the right parietal lobe. The insert shows the location of the abscess and the position of the drain.

Autopsy, performed sixteen hours post mortem by Dr. William R. Dodson, resident pathologist, disclosed extensive meningitis with greenish fibrinopurulent exudate most abundant over the right hemisphere and at the base of the brain. The brain was hardened and examined subsequently in the laboratory of neuropathology. The rubber catheter drain emerging from the lower end of the postcentral gyrus was still in place. The drain extended upward, medially and backward into a large, irregular, circumscribed but poorly encapsulated abscess occupying the right parietal centrum (fig. 1).

*Comment.*—This patient was at first suspected of having an intracranial tumor, a history of otitis media not having been elicited. When the patient became comatose and surgical intervention seemed urgent, a review of the history with his wife recalled to her the drainage from the right ear for two or three weeks at the beginning of the symptoms.

This made the diagnosis of abscess a definite probability. The occurrence of contralateral hemiplegia, the significance of which was not then understood, suggested a lesion higher and deeper in the hemisphere than the usual abscess of the temporal lobe.

The lesson which this patient's case taught had not been entirely forgotten when the next patient with similar symptoms and course, even though they were in a different setting, came under observation. The marked motor manifestations were the conspicuous and characteristic signs.

*CASE 5.—Bilateral otitis media following scarlet fever. Onset of jacksonian convulsions and right hemiparesis. Gradual recovery. Recurrence of hemiparesis after spells of vomiting two months later. Development of an irritable lethargic state. Negative exploration of the left temporal lobe. Later exploration and drainage of the left parietal lobe abscess. Recovery with residual jacksonian seizures.<sup>17</sup>*

A girl, aged 2½ years, was admitted to the Los Angeles County General Hospital on Dec. 4, 1931, with obvious scarlet fever of four days' duration. Four days later bilateral otitis media developed, and bilateral myringotomy revealed a purulent exudate in both middle ears. On December 23 a high temperature developed, and vomiting and jacksonian convulsions on the right side with conjugate deviation of the head and eyes to the right made their appearance. In the stuporous state which followed, right hemiplegia was noted. The spinal fluid was found to be bloody and under increased pressure. Because of cloudiness of both mastoids in the roentgenogram, bilateral mastoidectomy was done by Dr. Andrew Love. The uncovered dura was found to be normal in every respect. Culture of pus from the mastoid revealed *Streptococcus haemolyticus*. On the following day the child had roused somewhat but was aphasic and hemiparetic. The mastoidectomy wounds healed promptly, the paresis gradually improved and by the time of the patient's discharge on Jan. 30, 1932, she had apparently entirely recovered.

Because of the periodic bouts of vomiting and the difficulty in getting the child to take her food, her mother brought her to the hospital on February 24. After a period of observation the patient was found to be increasingly irritable and lethargic, and the optic disks gave evidence of increasing intracranial pressure. On the presumed diagnosis of abscess, the left temporal lobe was explored above and behind the ear on March 3 by one of us (Dr. Courville). The dura was found to be somewhat thinned, and the brain was under some pressure, but on repeated probings of the lobe the instrument failed to encounter either an abscess or the inferior horn of the ventricle.

The child seemed somewhat improved after recovery from the anesthetic. However, minor chills were noticed on two occasions, and spells of vomiting recurred. Three weeks later, because of increasing irritability and stupor, another exploration was decided on. A new opening was made farther forward toward the tip of the temporal lobe, and the brain was again explored with a needle. The tip of the inferior horn was entered, and the 3 or 4 cc. of slightly yellowish fluid which was recovered promptly coagulated. With the history of the previous case

---

17. This case has been presented in another connection in which was stressed the otitic etiology in certain instances of infantile hemiplegia (Concerning Certain Cerebral Manifestations Following Acute Otitis Media in Infancy and Early Childhood, *Am. J. Dis. Child.* 49:1 [Jan.] 1935). In this connection, repetition of clinical facts will be avoided, and certain surgical aspects will be emphasized.

in mind, the surgeon was prompted to explore the parietal lobe. A trephine opening revealed a very thin, transparent dura, evidently under considerable pressure. When the dura was opened a small knuckle of cortical tissue promptly herniated itself. The exploring needle encountered a heavily encapsulated abscess about 3 cm. beneath the cortex. A rubber tube drain was anchored in place. The nonfetid and greenish-yellow pus proved to be sterile. Figure 2 indicates the location of the three scars incident to the three explorations.

The child promptly recovered, and after three weeks the drain was removed. Repeated examinations revealed a residual weakness and clumsiness of the right extremities with persistent pathologic reflexes. There was some degree of mental



Fig. 2 (case 5).—Photograph showing three scars in the scalp over trephine openings in the skull. The dotted line shows the location and extent of each incision. The abscess was tapped through an opening over the parietal lobe. The scar of the original mastoidectomy incision is hidden by the auricula.

impairment, and the patient was unable to use formed words as before. She was discharged from the hospital on May 22.

On September 20 the child was brought in for reexamination, at which time the mother stated that there was some residual weakness in the right arm and leg, especially noticeable when the patient was tired. She had been rather wilful and difficult to control. There was some mental retardation, and the patient was still unable to talk. Three weeks later she was again brought in for examination with the report that she was having convulsive seizures affecting the right arm, apparently preceded by some painful or otherwise unpleasant sensations in this

member. The seizures continued for a number of months and were still present eighteen months after operation. Repeated examinations revealed evidences of a minor motor weakness in the right arm with characteristic reflex changes. She was reexamined on April 27, 1934, two years after drainage of the abscess. Some difficulty in talking was still present, and minor attacks of pain in the right arm were noted occasionally. Persistent pathologic reflexes were also noted on the right.

*Comment.*—This case represents the culmination of a series of experiences pertaining particularly to the pathology of otitic parietal abscess. It has led us to believe that a diagnosis of this lesion can be made at times and surgical treatment successfully instituted when conditions are favorable.

Our last experience was concerned with the postmortem findings in a case of otogenous parietal abscess. The record of this case was furnished through the courtesy of the attending physician.

*CASE 6.*—*Transient otitis media in a child three years before present illness. Headaches during the morning for two years. Onset of convulsions, left hemiplegia and coma. Death.*

A schoolgirl, aged 8 years, was first seen by Dr. Ben Anderson on March 13, 1934. The physician was called because the child had a convulsion following which she became stuporous. An inquiry into her history disclosed the fact that she had always been a semi-invalid because of a congenital pathologic condition of the heart. Three years before bilateral otitis media had developed following an attack of influenza, from which she recovered without incident after four weeks. For the past two years she had complained of headaches in the morning associated with ptosis of the right eyelid, both of which conditions improved as the day progressed. In the latter part of February 1934 she had an infection of the upper respiratory tract with fever, which persisted for several days. On March 8 she had a "spasm" and vomited, remaining in bed for the day. On March 12 she again became ill, complaining of severe headache in the right temporal region and ptosis of the right eyelid, associated with pain in the right eye.

Doctor Anderson found that the girl was semistuporous. The right eyelids were swollen and red. The right pupil was dilated. There were loud to-and-fro murmurs heard everywhere over the thorax but loudest over the base of the heart. The heart rate was irregular. The cyanosis and clubbed fingers were further indicative of a congenital cardiac lesion. There was complete left hemiplegia. The neck was rigid. A diagnosis of right parietal lobe abscess was made.

Lumbar puncture revealed a clear, colorless fluid under marked increase in pressure. There were 32 cells per cubic millimeter. There was no increase in globulin or sugar.

The child did poorly, and headaches, nausea and vomiting made their appearance. Convulsions recurred with periods of stupor. A few days before death the right eye became prominent, and Cheyne-Stokes respiration developed, associated with spasms of extensor rigidity. The right pupil was widely dilated, and the right disk was markedly swollen.

The patient was seen in consultation a few hours before death by Dr. Carl W. Rand, who found her in coma and having spasms of decerebrate rigidity. She died on March 27.

Autopsy was performed on the day of the patient's death by Doctor Anderson. As was suspected, a congenital lesion in the form of a defect in the intraventricular septum was found. The partially hardened right cerebral hemisphere was brought to this laboratory for study. The convolutions of this hemisphere were considerably flattened, particularly in the posterior parietal region. The superficial cerebral veins were markedly engorged but not thrombosed. In this region the cortex had been broken in the process of removing the brain from the skull. This had resulted in a rupture of the abscess and evacuation of its contents. This area appeared to be pale, and in it the small cortical vessels were empty. Beneath the torn cortex was found a thin-walled, empty capsule of an abscess. Its superficial portion was adherent to the overlying cortex beneath the terminal portion of several veins. The location and extent of the abscess and the appearance of its capsule are shown in figure 3.

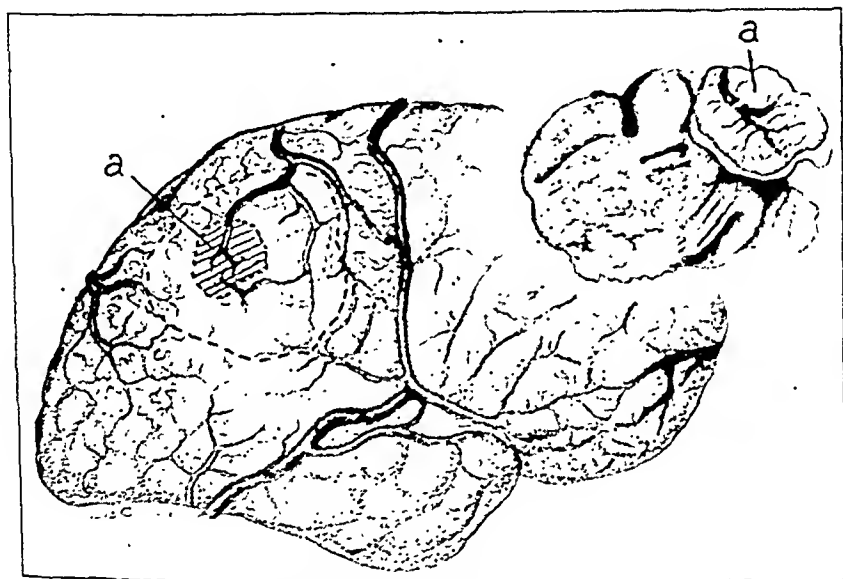


Fig. 3 (case 6).—Drawing of the brain, showing the appearance of the cortex in the parietal region. The shaded area (*a*) indicates the portion of the cortex attached to the capsule. The location of the abscess is indicated by the dotted line. The insert shows the collapsed capsule of the abscess.

*Comment.*—This unusual case did not come under our clinical observation, although it was our privilege to examine the brain and the contained abscess. From the long history of headaches during the morning and ptosis of the right lid, it is likely that the abscess resulted from the transient acute otitis media from which the patient had suffered three years before. This seems to be further proved by the fact that there had been no otitis media or other possible etiologic factor in the interim.

#### PATHOGENESIS

Since no previous effort has been made to study the group of otogenous abscesses of the parietal lobe as a whole, the pathogenesis



has not been elaborated on. A clue to the situation has been found in cases in which thrombosis of the lateral sinus is also present, a matter already dealt with in another connection.<sup>17</sup> As in the case of abscesses in other situations, there are a number of etiologic possibilities which must be considered (fig. 4). An otogenous parietal abscess may be secondary to: (1) an otogenous subdural abscess, (2) osteomyelitis of the parietal bone (which in turn is secondary to infection within the squamous portion of the temporal bone), (3) an otitic abscess in the temporal or frontal lobe or (4) thrombosis of the venous channels or

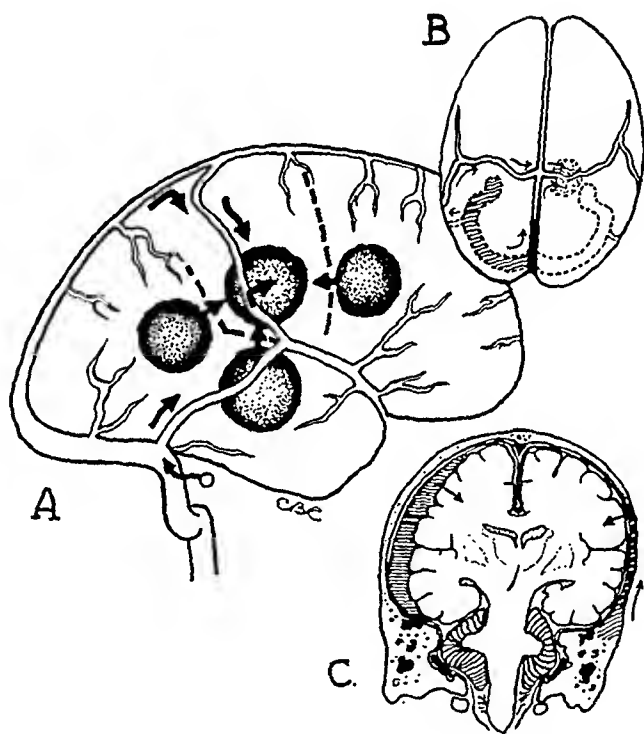


Fig. 4.—Drawing showing the possible pathways of infection from the middle ear to the parietal lobe. *A* illustrates the development of the parietal abscess by extension along the venous channels or the development secondary to the otitic abscess in the other lobes; *B*, an insert, shows the possible pathways of a parietal abscess in the hemisphere opposite the draining ear, although such an abscess may be due to an apparently unaffected ear on the same side, and *C*, an insert, shows the situations which may theoretically result in a parietal abscess—a subdural abscess on the left and osteomyelitis of the squama of the temporal and the parietal bones on the right.

extension along these channels without grossly visible thrombus formation.

The possible development of a parietal abscess from an extension into the brain of infection from an overlying subdural abscess must be considered, particularly since this lesion has been found to be present in

a number of the cases. On rare occasions it is found that an abscess secondary to empyema of the frontal sinuses is located at some distance from the point of invasion of the intracranial space. Examination of the brain in these cases reveals an extensive obliteration of the subdural space, evidently due to a resolved subdural infection, perhaps of low grade virulence. While the same possibility must be admitted in this connection, no clearcut case has yet been described. In the group of cases reported in the literature a subdural abscess was found in 2 (Lubliner<sup>9</sup> and Bryan<sup>12</sup>). It was also present in 1 of our cases (case 3). While proof either for or against this conception would be difficult to find, it seems to us unlikely that intracerebral abscess results from acute subdural abscess. In the last analysis it is more likely a question of coincident lesions having the same source.

It is also possible that osteomyelitis of the parietal bone secondary to an otogenous infection in the squamous portion of the temporal bone might result in the formation of a parietal abscess. Local adhesion to the leptomeninges in the parietal region would pave the way for invasion of the brain substance. The situation is a most unusual one, and it is not likely that many cases of parietal abscess will be accounted for on this basis. No such example has been reported in the literature.

The development of a parietal abscess secondary to one located in either the temporal or the frontal lobe is a matter of rare chance. Such an abscess in reality is one of several cavities of a multilocular abscess and communicates by a fistulous tract with the parent abscess. It is usually the result of a secondary extension through a weakened spot in the capsule of the original abscess. Lubliner<sup>9</sup> reported a unique case in which an otitic abscess in the left temporal lobe was drained surgically. A recurrence of symptoms brought about the patient's death. At autopsy it was found that the first abscess communicated with a second located above the sylvian fissure by means of a fistulous channel. Coates and Case<sup>11</sup> reported a somewhat similar case in which an otogenous abscess of the frontal lobe communicated with another cavity in the parietal lobe.<sup>10</sup>

It is obvious that abscesses developing in any of the foregoing ways are pathologic rarities and occur as a matter of chance. Invasion by way of vascular channels seems to explain the occurrence of the greater number of them.

The proposition that these distant abscesses are the result of spread of infection by way of the arterial tree has met with considerable favor in some circles. This requires as a preliminary step either (*a*) the development of a periarterial infection, secondary arteritis and extension into the lumen of the carotid artery or (*b*) an invasion of the venous channels of the middle ear and extension into the lateral sinus, resulting

in a systemic infection. The relative rarity of pericarotid infection and the fact that such an infection causing either arteritis or thrombosis practically never results in the formation of a cerebral abscess seems to rule out the first possibility. Furthermore, the absence of typical septic manifestations and of other localized foci elsewhere in the body and the frequent occurrence of a solitary cerebral abscess under the circumstances seriously controvert the second conception.

On the other hand, there is convincing evidence at hand to indicate that extension occurs, in many cases at least, by venous channels. A possible mechanism is suggested by the occurrence at times of cerebral symptoms in cases of thrombosis of the lateral sinus. These manifestations are presumed to be due to a stasis in the inferior anastomotic and occipital veins and their communicating vessels.<sup>18</sup> When the parietal abscess occurs in a case in which there is a continuous thrombosis from the lateral sinus into the inferior cerebral or communicating veins leading to the parietal region, the mechanism of the spread of infection is obvious.

Furthermore, when there has been thrombosis of the venous network of the dorsolateral surface of the brain without involvement of the lateral sinus or, on the other hand, of the lateral sinus without involvement of the veins, the likelihood of extension even in the presence of a break in the chain of the thrombosed vessels must still be granted. This possibility still exists when the venous system is not found to be grossly involved at autopsy. It is our belief that a small thrombus responsible for localization of the infection may resolve, while the infection in the brain substance goes on to the formation of an abscess. The various degrees of involvement of the venous channels as illustrated by the reported cases is shown in figure 5.

The actual method of production of the abscess following venous thrombosis is not entirely clear. Hlaváček<sup>19</sup> predicated a perivenous infarct as the mechanism which might produce under suitable circum-

---

18. This conception is substantiated by clinical evidence which also suggests that there is some relationship between thrombosis of the lateral sinus and the occurrence of manifestations in the parietal lobe. This question has recently been studied by Bodechtel and Richter (*Ueber Scheitellappensymptome beim otogener Thrombophlebitis der Gegenseite*, *Ztschr. f. Hals-, Nasen- u. Ohrenh.* **32**:505, 1913). The presence of symptoms referable to the central region in these instances suggests that obstruction of the venous flow into the lateral sinus from this region, particularly in the presence of an infectious condition, is accompanied by a disturbance in the circulation (edema). If more critical neurologic examinations were made in all cases of thrombosis of the lateral sinus, minor evidences of this disturbance would frequently be found. This has been the experience of the writers.

19. Hlaváček, V.: *Časop. lék. česk.* **2**:1041 (July 11) 1930; cited by Eagleton, W. P.: *Arch. Otolaryng.* **16**:228 (Aug.) 1932.

stances an abscess on the one hand or meningitis on the other. It is likely that either a focus of red softening occurs which becomes infected or a primary focus of infection develops in the subcortical white substance along an afferent vein. The occurrence of a variety of lesions and of different anatomic types of abscess suggests that invasion may take place in one of several ways.

The pathogenesis of multiple abscesses is of particular interest. The occurrence of multiple foci has been accepted by many as presumptive

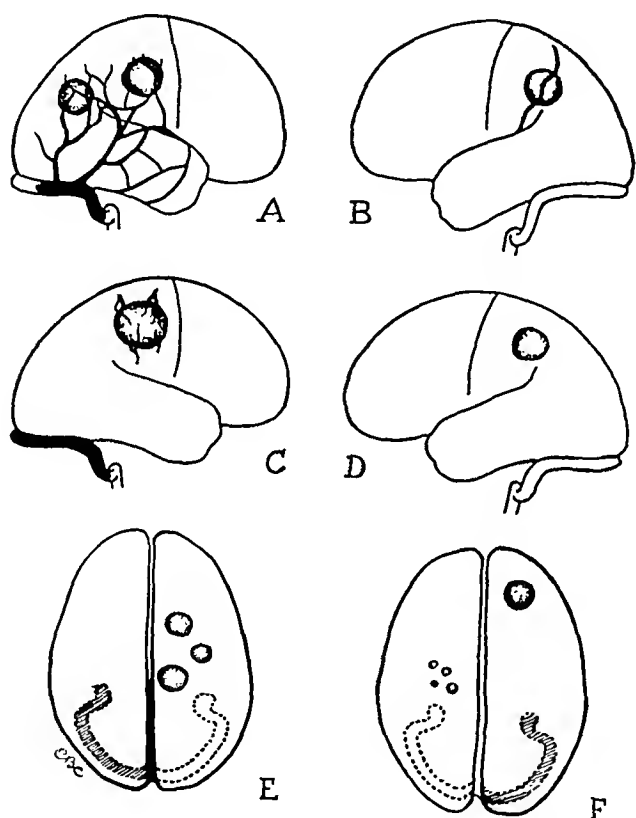


Fig. 5.—Drawing showing the relationship of thrombosis of the venous channels to abscess of the parietal lobe, as illustrated by lesions found in various cases. *A* (case of Faunce and Shambaugh<sup>14</sup>) illustrates thrombosis of the right lateral sinus and the afferent veins; *B* (case of Pitt<sup>5</sup>), thrombosis of the superficial cerebral vein (probably the vena anastomotica major); *C* (case 3 of our series), thrombosis of the right lateral sinus and the veins over the abscess (in the latter situation thrombosis was possibly due to the underlying infection); *D* (case of Westphal), thrombosis which did not affect any of the venous channels (verified by autopsy); *E* (second case of Pitt), thrombosis of the contralateral (left) lateral sinus and posterior portion of the superior longitudinal sinus and multiple abscesses of the centrum ovale; *F* (case of Urbantschitsch<sup>13</sup>), thrombosis of the contralateral (right) lateral sinus, multiple small abscesses of the left parietal lobe and solitary abscess of the right frontal lobe.

evidence of their metastatic (arterial) origin. According to the evidence at hand, this is not necessarily true. In the case of Faunce and Shambaugh<sup>14</sup> this is obviously not the case, for the 2 abscesses in the parieto-occipital region were located immediately beneath the network of thrombosed superficial veins. We believe that in many instances of multiple abscess there may be no gross residual evidence of involvement of the venous channels. When an abscess formation in the temporal lobe is one of multiple abscesses, it may be due to extension by contiguity rather than by way of the venous channels. Thus two distinct modes of spread may be present in a single case. While it is not certain, this may have been the situation in Bryan's case.<sup>15</sup> In 1 of our cases (case 3) there was a local fistula in the tegmen, dura and brain but a subdural rather than a temporal abscess.

#### PATHOLOGY

A study of the histologic characteristics of otogenous abscess of the parietal lobe is not of paramount interest in this connection, since they are much the same as those of abscess in other situations. Certain deductions may be drawn, however, from the morbid anatomy, which sheds light on the problem of cerebral abscess as a whole.

The anatomic types of abscess found in the parietal lobe are the same as those that occur elsewhere. The large acute abscess, otherwise known as purulent encephalitis, with its poorly defined margins and necrotic center, is exemplified by case 3 of our series. In later stages of this same anatomic variety, suppuration occurs in the central portion of the involved region, and its walls are ragged, necrotic and stained at times with hemorrhage. The surrounding cerebral tissue is edematous, swollen and infiltrated with pus. It is this type of abscess which has a short clinical course and is evidently the result of invasion of a virulent organism against which the body has little resistance.

The more slowly developing, circumscribed but poorly encapsulated abscess is usually unilocular, with sharply defined walls. The surrounding zone of encephalitis varies in width with the acuteness of the process. In this type, the thinness of the wall of connective tissue is due, in part at least, to the large size of the cavity and not alone to the low resistance against the infection. Cases 2 and 4 are examples of this anatomic type. This variety of abscess yields a large amount of pus when tapped at operation, and if drainage is properly instituted a cure may be attained, at times with certain residual manifestations. When the abscess is not drained the patient often succumbs with respiratory failure, death being due to the greatly increased intracranial pressure. The history in case 6 suggests that these abscesses, though large, may acquire a capsule and remain partially quiescent for months and even years.

The classic small, heavily encapsulated abscess may occur here as typically as in the temporal lobe. The cavity is usually small or of moderate size. Theoretically, an abscess of the parietal lobe may be multiloculated, as may one in the temporal lobe, but no case of this type has been described.<sup>20</sup> The thick capsule is usually an indication of a more chronic and avirulent infection in a circumscribed focus. This type of abscess, perhaps the most favorable for surgical treatment, may be drained as successfully when located in the parietal as when located in the temporal lobe, provided it is uncomplicated. This seems to be proved by our experience in case 5 of this series.

Perhaps the most important conclusion to be drawn from the fact that any anatomic variety of abscess may occur in the parietal lobe is that the type of abscess does not depend on the method by which the infection reaches the brain. This may be concluded from the fact that abscesses in the temporal lobe are for the most part due to contiguous infection of the bone, dura and brain, while those of the parietal lobe are commonly the result of vascular extension. It is therefore likely that the anatomic type of otogenous abscess produced is the result of the virulence and number of invading organisms or is of the nature of a presumed preliminary (vascular) lesion which becomes secondarily infected. It is possible that both factors play a variable rôle.

As has already been indicated in a review of the literature, an abscess of the parietal lobe may constitute one of a group of multilocular abscesses, being connected by means of a fistulous tract with other cavities in the temporal or frontal lobe (Harris,<sup>5</sup> Lubliner<sup>9</sup> and Coates and Case<sup>11</sup>). In such instances the clinical picture is complicated and almost impossible to evaluate properly. In the case of Urbantschitsch<sup>13</sup> one group of small abscesses was found in the left parietal lobe while another larger abscess was found in the left frontal lobe. The case of Faunce and Shambaugh<sup>14</sup> is of interest in that two abscesses (one parietal and the other parieto-occipital) had their origin in an extensive thrombosis of the dorsolateral venous system. In the cases forming our series, no case of multiple abscess was disclosed.

As one might suspect from the origin of the abscess, adherence of the capsule to the altered overlying cortex is at times observed. This was illustrated in our sixth case. The infection arising from local venous thrombosis extends through the altered cortex, and the resulting reaction of the connective tissue binds the capsule to the pia and its vessels.

---

20. The case of Urbantschitsch<sup>13</sup> is of interest in that there were several small abscesses in the left parietal lobe and another larger one in the right frontal lobe. The description furnished by this observer was too meager to ascertain whether the abscesses were distinct cavities or whether they were multiple loculations of a single focus of infection. One would infer that the former was the case.

As in instances of abscess of the temporal lobe, rupture into the lateral ventricle may occur. In this case the abscess must break through the intermingled fibers of the corona radiata to burst into the lateral margin of the body of the ventricle or through the corpus callosum to break through its roof. In one of Holt's<sup>6</sup> cases rupture into the ventricle had taken place, and in the other the abscess extended to the ependymal lining but gross rupture had not occurred. In Bryan's<sup>15</sup> case the temporal abscess had ruptured into the ventricle while the abscess in the parietal lobe had not. There was no instance of rupture into the ventricle in our series.

The changes in the surrounding brain as a result of the presence of the abscess are of interest. The overlying convolutions are found to be flattened and the lobe enlarged, as is the case with an abscess in any situation. Streaks of exudate are frequently found along the vessels of the cortex overlying the abscess, a finding not so commonly observed in cases of abscess of the temporal lobe.

The overlying vessels are at times thrombosed. This is of particular significance in this connection, for in many instances the thrombosed veins are part of a widespread involvement of the venous system of the dorsolateral surface (Faunce and Shambaugh<sup>14</sup>), of some isolated vessel (Pitt<sup>5</sup>) or of the lateral sinus (Pitt,<sup>5</sup> Uchermann,<sup>12</sup> Urbantschitsch<sup>13</sup> and case 3 of this series). At times the opposite lateral sinus or its afferent vessels are found to be thrombosed (the second case of Evans<sup>4</sup> and the second case of Pitt<sup>5</sup>). The significance of thrombosis of the venous channels has been discussed in the previous section.

A subdural abscess has been found to be present in a number of instances. This lesion was disclosed at a previous operation in Lubliner's case<sup>9</sup> and in case 3 of our series and at autopsy in Bryan's case.<sup>15</sup> The subdural collection of pus is probably a coincident lesion, arising separately from the original infection in the middle ear or secondary to thrombosis of the lateral sinus.<sup>21</sup> It is rarely due to rupture of a cerebral abscess through the adherent leptomeninges into the subdural space. This has not occurred in any of the reported instances of otogenous abscess of the parietal lobe.

#### CLINICAL ASPECTS OF OTOGENOUS ABSCESS OF THE PARIETAL LOBE

As the result of our experience in dealing with vascular or infectious lesions of the dorsolateral surface of the hemisphere we have come to

---

21. The matter of otogenous subdural abscess is one of unusual interest. Following thrombosis of the lateral sinus it may be found in a variety of situations. The question has been briefly discussed in a previous communication (*Fatal Complications of Otitis Media, with Particular Reference to the Intracranial Lesions in a Series of Ten Thousand Autopsies*, Arch. Otolaryng. 19:451 [April] 1934), and a more detailed study is made the subject of a forthcoming review.

believe that their diagnosis constitutes a neurologic problem capable of solution. From a therapeutic standpoint an accurate localizing diagnosis is essential to successful drainage of the abscess. Should such an abscess be tapped by chance through a high temporal trephine opening, the angle which the tube assumes makes continuous drainage unlikely or dislocates it from its original position in the abscess cavity. Furthermore, it may so lacerate the brain tissue that drainage occurs about the tube with a resultant septic meningitis. If, on the other hand, one can approach the abscess through a trephine opening directly over it, the matter of drainages becomes a more simple problem, provided, of course, the abscess is encapsulated or at least circumscribed.

It is evident that the symptoms produced by an expanding lesion differ considerably from those of a purely local and destructive one. An abscess situated within the limits of the parietal lobe may, as a result of pressure, consequent edema or actual extension, so disturb the function of adjoining regions as to result in symptoms referable to these areas.<sup>22</sup>

We shall therefore find it necessary in cases of parietal abscess to consider some symptoms which have long been attributed to other cortical areas. Needless to say, the limitations of the subject at hand preclude a complete discussion of the symptomatology of lesions of the parietal lobe. We shall confine ourselves, therefore, to the essentials which are of value in the diagnosis of parietal abscess. Unfortunately, in almost all of the reported cases the situation of the lesion was misinterpreted or the case report so brief that one is unable to draw any conclusions as to their neurologic symptomatology.

The irritative motor symptoms are characteristically jacksonian seizures affecting the contralateral side of the body but particularly the upper extremity and face. These symptoms are at times observed in infants and young children with otitis media, and in most instances recovery is complete. Whether or not the occurrence of these symptoms signifies the development of an abscess can be determined only

---

22. The wide variety of otogenous lesions, whether toxic, vascular or inflammatory, which affect the dorsolateral surface of the brain are probably the result of an extension of the noxious agent along venous channels from the middle ear.<sup>17</sup> The location and extent of the ultimate lesion are due in part to the pattern of the venous channels draining this area. The inferior anastomotic vein, which serves as the connecting link between the venous radicals draining the middle ear and the dorsolateral venous system, may empty into the superficial middle cerebral vein at any point along its course. This exposes to the influence of the noxious agent the posterior surface of the frontal as well as the parietal lobe. The marked motor as well as sensory manifestations so often present in these cases suggest that this area is actually affected. From a clinicopathologic point of view it seems best to designate this area as paracentral, although it is not to be confused with the paracentral lobule on the medial surface of the hemisphere.



by watching carefully the clinical course of the illness. In the first known reported cases of Pitt<sup>5</sup> typical jacksonian seizures were described. In a recent contribution on cerebral abscess Atkinson<sup>23</sup> stated that jacksonian seizures are characteristic of lesions of the parietal lobe. Unfortunately in the earlier cases in our series complete clinical histories were not available, so it could not be ascertained whether the symptoms occurred. The first patient (case 4) to come to our attention was said to have had convulsions of a generalized character with subsequent deviation of the head and eyes and contralateral hemiplegia. One patient (case 5) had characteristic contralateral jacksonian seizures with involvement particularly of the arm and face.

Conjugate deviation of the head and eyes as a symptom of lesions of the posterior and inferior portion of the parietal lobe was first described by Landouzy<sup>24</sup> in 1879 and has been confirmed many times since. It was the subject of a recent contribution by Meyers<sup>16</sup> from the Los Angeles County General Hospital. When deviation occurs as a part of the seizure, the head and eyes are directed toward the convulsing members and away from the side of the lesion (case 5). Later, when paralysis has set in, the deviation is toward the side of the lesion (case 4). In either case deviation may be of so minor a degree as to be overlooked or may be absent altogether.

Paralytic motor phenomena made their appearance in all of the cases which were observed personally but have not been recorded in most of the reported cases. No doubt minor manifestations of weakness have been overlooked in young children or in adults in a terminal state. In case 3 weakness was observed only by chance just before surgical exploration. In case 4 it developed after "generalized" convulsions and was associated with conjugate deviation of the head and eyes toward the side of the lesion and away from the paralyzed members. In case 5, that of a child aged 2½ years, the right jacksonian seizures observed at the onset were followed by right hemiplegia, most marked in the arm and face. These manifestations slowly disappeared but reappeared when signs of pressure became evident. This suggests that motor symptoms are due to irritation or pressure on the precentral gyrus. In case 6 preterminal contralateral hemiplegia was noted.

Sensory disturbances have long been recognized as primary parietal manifestations. The postcentral and perhaps adjacent cortex integrate the various sensory impressions from the opposite side of the body and

---

23. Atkinson, E. M.: Abscess of the Brain; Its Pathology, Diagnosis and Treatment, *Lancet* 1:486 (March 10) 1928.

24. Landouzy, L.: De la déviation conjuguée des yeux et de la rotation de la tête, etc., *Bull. Soc. anat. de Paris* 4:293 (April 18) 1879; cited by Charcot, J. M., and Pitres, A.: Etude critique et clinique de la doctrine des localisations motrices, Paris, Germer, Baillière et Cie, 1883.

fuse them into a whole whereby a person is able by touch to recognize the size, shape, weight and texture of objects placed in his hand. In this function the proprioceptive sense probably plays a leading rôle.<sup>25</sup> In the lesions of the parietal lobe, the patient experiences a decreased sensibility for all modalities without loss of any except tactile discrimination (astereognosis). In case 4 there was a history of paresthesia and numbness of the left extremities, beginning in the foot, if the record is correct. On examination there was hyperesthesia of the entire left side of the body. Because of mental torpor and decreased sensibility, a true estimate of stereognosis could not be reached. In case 5 because of the patient's age (2½ years) sensory changes could not be detected. Later, however, the appearance of minor seizures on the right side seemed to be heralded by sensory manifestations. The child would grasp the right arm and cry out in distress before the motor manifestations became apparent.

Trophic changes in the form of atrophy of the muscles of the contralateral extremities from parietal lesions in early life have been described by von Monakow.<sup>26</sup> This observation has been made recently by Silverstein<sup>27</sup> in a case of tumor of the parietal lobe. Most patients with parietal abscess do not survive long enough to enable one to determine whether or not atrophy occurs. In case 5 it had not occurred in the limbs affected during the acute stage of the abscess as late as two years after successful surgical drainage.

Vasomotor disturbances have also been described by von Monakow in cases of lesions of the parietal lobe. It is of interest to note that in 1 of our cases the skin of the contralateral side was warmer to touch and that perspiration was obviously increased on that side. It is possible that these manifestations are not in themselves evidences of parietal dysfunction.

Hemianopia has been described by various observers in instances of parietal lesions. In cases of tumor or abscess of the parietal region it is easily possible that the subjacent optic radiation is influenced by pressure or extension. This manifestation has not been observed in any of our cases.

Disturbances of speech in cases of lesions of the cortex or sub-cortex of the parietal lobe constitute too large a subject for detailed discussion in this connection. Mind blindness, alexia, agraphia, apraxia

25. Kramer, F.: Die kortikale Tastlähmung, *Monatschr. f. Psychiat. u. Neurol.* 19:129, 1906.

26. von Monakow, C.: *Gehirnpathologie*, Vienna, Alfred Hölder, 1905, p. 683.

27. Silverstein, A.: A Tumor of the Parietal Lobe Showing Jacksonian Sensory Seizures Involving the Tongue, Face, Thumb and Index Fingers with Advanced Premature Atrophy of the Affected Parts, *J. Nerv. & Ment. Dis.* 77:371 (April) 1933.

and disorientation have all been described. The size and exact situation of an abscess and the extent of involvement of surrounding cerebral tissue by encephalitis or edema have much to do with the manifestations presented.

Of the various possibilities the one of particular interest is that of mind blindness, a subject introduced by Munk after a study of experimental cortical lesions in dogs. This has been greatly elaborated on by Pötzl.<sup>28</sup> A person so affected is able to see clearly but fails to recognize even the most familiar faces and objects. He is therefore disoriented and helpless. He necessarily has sensory apraxia, for he fails to recognize the use of objects which he cannot identify. Thomas<sup>29</sup> reported a case in which the patient "forgot" the affected extremities. A true paralysis did not exist, but the patient did not use the affected extremities because he was unaware of their presence. This manifestation, not observed in any of our cases, can be distinguished from paralysis if one calls the patient's attention to these members and asks him to move them. Amnesic aphasia, affecting most often and most seriously the memory for names, is quite a common finding in association with lesions of the inferior parietal lobule.

Disturbance of consciousness is a common manifestation of cerebral abscess usually attributed to increased intracranial pressure. However, in cases of lesions of the parietal lobe, repeated periods of unconsciousness have been described. We have not been able to determine whether this is any more true of parietal than of temporal abscess. It would be a difficult matter to settle this question when the parietal lesion is an abscess, since fluctuations in the degree of consciousness are a common accompaniment of abscess of the brain in any situation.

#### SUMMARY

The parietal lobe has been said to be the most unusual location for an abscess secondary to otitis media. A review of the literature would seem to substantiate this claim, although many abscesses in this situation have been miscalled as far as location is concerned.

A series of 6 cases has come to our attention. Three of these were discovered in a review of 10,000 records made at autopsy. Two other cases were studied clinically as well; 1 terminated fatally after exploration and in the other a correct diagnosis was made and the abscess was successfully drained. In the last case, a study was made of the brain, which was brought to our laboratory by the attending physician, who also furnished us with the clinical history.

---

28. Pötzl, O.: *Die Aphasielehre vom Standpunkte der klinischen Psychiatric*, Leipzig, Franz Deuticke, 1928, vol. 1.

29. Thomas, cited without reference by Claude, H.: *Maladies du système nerveux*, ed. 2, Paris, J. B. Baillière et fils, 1932, p. 435.

The distance between the middle ear and the parietal lobe predicates in most instances a vascular route for the transmission of the infection. The arterial route has been quite widely accepted as the one of choice. The frequent association of thrombosis of the lateral sinus and of other associated venous channels has led us to believe that invasion occurs by this route instead. Infection enters the venous radicals draining the middle ear and, with or without gross occlusion of the veins, extends to the parietal or other regions.

The same anatomic type of abscess may occur in the parietal as in the temporal lobe, i. e., (1) acute diffuse abscess, (2) large circumscribed abscess and (3) small encapsulated abscess. The vascular and other inflammatory lesions secondary to otitis media may occur here as well as in other parts of the brain.

Otogenous abscess of the parietal lobe is frequently associated with one or two or more cerebral abscesses, which results in a complex clinical picture. It is at times associated with subdural abscess. In most of the reported cases the abscess has occurred on the left side of the brain.

The characteristic symptoms of abscess of the parietal lobe thus far determined are jacksonian seizures affecting the contralateral members, often associated with deviation of the head toward the convulsing members, followed by monoplegia brachiofacialis, deviation away from the paralyzed side, sensory manifestations and at times aphasia.

The incompleteness of the knowledge of the pathologic and clinical picture calls for a more critical study of every potential case and a careful examination of the system of connected venous channels of the brain should the case terminate fatally. More complete clinical records in such instances are necessary.

# DIAGNOSIS OF NEUROGENIC LESIONS OF THE URINARY BLADDER BY CYSTOMETRY

AN APPRAISAL OF THE METHOD BASED ON EXPERIMENTATION  
WITH ANIMALS

J. M. McCAUGHAN, M.D.

AND

J. H. HERSHEY, M.D.

ST. LOUIS

In clinical urology Rose and his co-workers<sup>1</sup> made studies of the urinary bladder by means of the cystometer, an instrument which records synchronously the intracystic capacity and pressure. The results seemed to indicate that valuable diagnostic criteria with respect to neurogenic lesions of the bladder could be obtained in this manner. These investigators classified neurogenic dysfunctions of the bladder cystometrically into those caused by (1) irritation or destruction of the sympathetic, (2) irritation or destruction of the parasympathetic, (3) interference with the function of the nervus pudendus, (4) lesions of the central nervous system above the origin of the thoracolumbar (second dorsal) spinal segment, (5) psychic (hysterical) bladder, (6) reflex mechanism seen in cases of postoperative retention and (7) intraspinal or extraspinal injury provided the lesion affects one of the reflex areas of innervation of the bladder.

In general, cystometric curves were interpreted as representing parasympathetic or sympathetic overbalance if abnormal pressure and capacity were encountered. In the case of a destructive lesion of the sympathetic (1 in the classification) one expected to find abnormally low intracystic capacity and unusually high intracystic pressure. In the case of a destructive lesion of the parasympathetic (section 2 in the classification) the reverse effects were expected. Irritative lesions, on the other hand, were presumed to produce an imbalance simply as a result of the overstimulation of one side or the other of the autonomic

---

From the Department of Experimental Surgery, St. Louis University School of Medicine.

1. (a) Rose, D. K.: Cystometric Bladder Pressure Determinations: Their Clinical Importance, *J. Urol.* **17**:487 (May) 1927. (b) Rose, D. K., and Deakin, R.: A Cystometric Study of the Pharmacology of the Bladder, *Surg., Gynec. & Obst.* **46**:221 (Feb.) 1928; (c) The Cystometric Diagnosis of Central Nervous System Syphilis: A New Appreciation of the Term Neurogenic Bladder, *Am. J. Syph.* **12**:3 (July) 1929. (d) Rose, D. K.: Clinical Application of Bladder Physiology, *J. Urol.* **26**:91 (July) 1931. (e) Rose, D. K., and Rollins, P. R.: Pyelonephritis in Pregnancy: Its Treatment and Prevention Based on Cystometric Conclusions, *J. A. M. A.* **96**:231 (Jan. 24) 1931.

system, and the effects observed cystometrically were believed to reflect this disturbance by varying the capacity and pressure within the bladder. Other factors not of neurogenic origin, however, entered into the final analysis of cystometric records, particularly the coexistence of such pathologic conditions as obstruction of the neck of the bladder, urethritis, cystitis and cystocele.

McCaughan, Major and Braasch<sup>2</sup> reported a group of eighty cases in which they attempted to correlate data from the cystometric, cystoscopic and neurologic examinations in order to evaluate the cystometric data; they came to the conclusion that cystometry is only occasionally of positive value without other corroboratory data, either clinical or cystoscopic. Watkins,<sup>3</sup> using somewhat similar methods, came to a similar conclusion.

The present experiments were carried out on dogs in conjunction with other studies reported elsewhere<sup>4</sup> on the effects of sympathetic and parasympathetic denervation on the tons of the rectum, colon and bladder. It seemed interesting at the same time to investigate the condition of the urinary bladder in manesthetized dogs by means of cystometry before, and at varying intervals after, such operative procedures as bilateral sympathectomy, parasympathectomy, hypogastric gangliectomy, resection of the pudic nerve and transverse division of the spinal cord at various levels. It seemed likely that certain difficulties in our experience with the interpretation of clinical cystometrograms might be overcome by an analysis of cystometric records obtained for animals in which definite lesions of the nerve supply to the urinary bladder had been produced experimentally.

There are a number of theoretical and practical objections inherent in the instrument as well as in the technic of its application: 1. The intermittent action of the pump causes the water to be ejected suddenly and produces a notched or toothed curve rather than a smooth one. 2. It is difficult to keep the valves clean, particularly if isotonic salt solutions are used; this is important because the clogging of the valves which invariably follows causes inaccuracies in the volume output of the pump. 3. It is somewhat troublesome to maintain proper sterilization of the apparatus. 4. The use of air in the inlet or pressure-recording system is scientifically objectionable because of the great compressibility of air.

---

2. McCaughan, J. M.; Major, S. G., and Braasch, W. J.: Value of the Rose Cystometer in the Diagnosis of Neurogenic Affections of the Urinary Bladder in Man, *J. Urol.* **27**:229 (Feb.) 1932.

3. Watkins, K. H.: Personal communication.

4. Hershey, J. H., and McCaughan, J. M.: Surgery of the Autonomic Nervous System: I. The Effect of Parasympathetic Denervation on the Rectum and the Colon (Experimental Megacolon), *J. Missouri M. A.* **31**:413 (Nov.) 1934; II. The Effect of Sympathetic and Parasympathetic Denervation on the Urinary Bladder, *ibid.* **31**:417 (Nov.) 1934.

5. The rate at which the bladder is filled has not been adequately standardized. 6. There is no satisfactory means of controlling the temperature of the fluid in the reservoir. 7. In a sensitive or inflamed urethra or bladder, the irritation by catheter produces myogenic effects difficult to differentiate from the purely neurogenic effects. 8. In human beings value of the data based on subjective sensory experience varies greatly with the general level of intelligence and with the emotions. Nevertheless, a more important consideration is to be found in experimental data of numerous investigators with regard to the neurophysiology of the urinary bladder. For example, a review of the literature on the physiology of the urinary bladder recently published by Gruber<sup>5</sup> emphasizes the fact that although the bladder is innervated by both the sympathetic and the parasympathetic system each nerve supplies impulses which are both motor and inhibitory, and there seems to be little difference in the effects of the two systems except that the impulses of the parasympathetic nerves are perhaps stronger. MacDonald and McCrea<sup>6</sup> made similar observations with respect to gastric innervation, but of especial interest in this connection is the work of Potter,<sup>7</sup> who determined the intravesical pressures in unanesthetized dogs at varying intervals after parasympathetic denervation of the urinary bladder and found that they were the same as the preoperative readings.

On the other hand, there is some evidence to support a belief in permanent neurogenic imbalance as a consequence of destructive lesions of autonomic nerves. Adamson and Aird<sup>8</sup> reported the experimental production of megacolon by the division of the pelvic nerves in cats. This work recently has been confirmed by McCaughan and Hershey for cats, but in dogs the evidence was not so convincing. Variations among individuals and species, however, are not uncommon.<sup>9</sup> Furthermore, Learmonth<sup>10</sup> reported favorable results from division of pre-

---

5. Gruber, C. M.: The Autonomic Innervation of the Genito-Urinary System, *Physiol. Rev.* **13**:497 (Oct.) 1933.

6. MacDonald, A. D., and McCrea, E. D.: Observations on the Control of the Bladder: The Effects of Nervous Stimulation and of Drugs, *Quart. J. Exper. Physiol.* **20**:379, 1930.

7. Potter, J. C.: The Effects of Section of Both Sacral Nerves on Intravesical Pressure, *J. Urol.* **15**:197 (Feb.) 1926.

8. Adamson, W. A. D., and Aird, I.: Megacolon: Evidence in Favor of a Neurogenic Origin, *Brit. J. Surg.* **20**:220, 1932.

9. Elliott, T. R.: The Innervation of the Bladder and Urethra, *J. Physiol.* **32**:367, 1906-1907.

10. Learmonth, J. R., and Braasch, W. F.: Resection of the Presacral Nerve in the Treatment of Cord Bladder: Preliminary Report, *Surg., Gynec. & Obst.* **51**:494 (Oct.) 1930. Learmonth, J. R.: A Contribution to the Neurophysiology of the Urinary Bladder in the Human Being, *Brain* **54**:147 (June) 1931. Learmonth, J. R.; Montgomery, H., and Counseller, V. S.: Resection of the Sensory Nerves of the Perineum in Certain Irritative Conditions of the External Genitalia, *Arch. Surg.* **26**:50 (Jan.) 1933.

sumably overacting autonomic nerves for the relief of neurogenic imbalance of the urinary bladder in human beings. However, the relative importance of destructive as compared with irritative lesions in the pathogenesis of neurogenic dysfunction of the bladder is not well known. In the experiments reported here the lesions were all destructive.

#### EXPERIMENTAL PROCEDURE

Female dogs of approximately similar weight and of docile disposition were chosen for training. The animals were catheterized repeatedly before operation, and cystometric readings were taken. It was found possible to train the animals

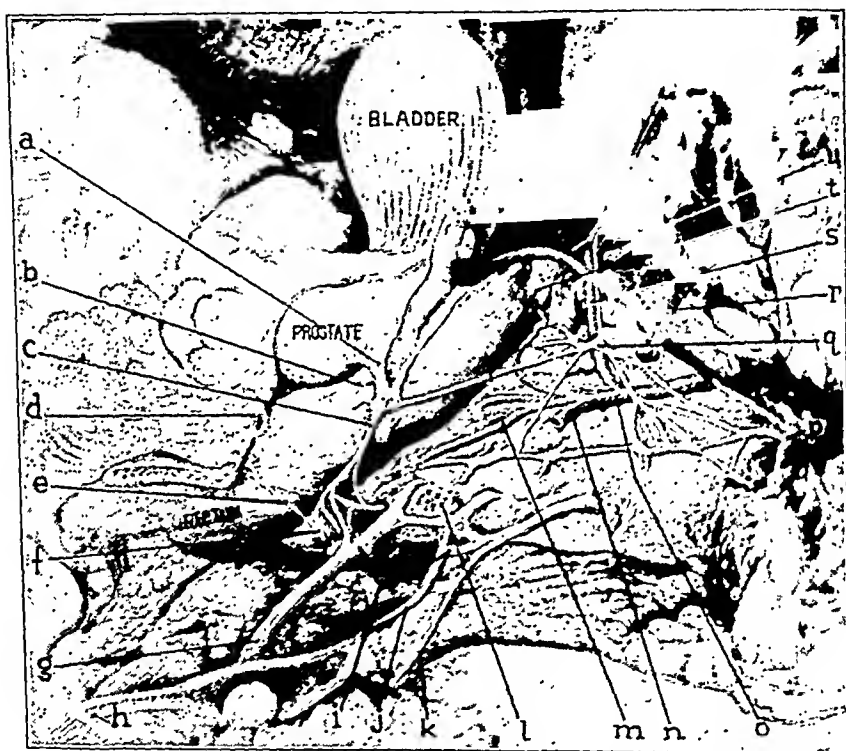


Fig. 1.—Neuro-anatomy of the rectum, colon and bladder in the dog. The pelvic plexus is indicated by *a*; the sympathetic and parasympathetic fibers to the bladder, rectum and descending colon, by *b*; the pelvic nerve, by *c*; the pubic ramus, by *d*; the pudic nerve, by *e*; the sacral plexus (first, second and third sacral roots), by *f*; the sciatic nerve, by *g*; the ileum, by *h*; the lumbar plexus, by *i*; the obturator nerve, by *j*; the femoral nerve, by *k*; the promontory of the sacrum, by *l*; the internal iliac artery, by *m*; the external iliac artery by *n*; the abdominal aorta, by *o*; the lumbar sympathetic chain, by *p*; the inferior mesenteric ganglion, by *q*; the ureter, by *r*; the inferior mesenteric artery by *s*; the hypogastric nerve, by *t*, and the lumbocolonic nerve, by *u*.

to submit easily to catheterization and to lie quietly while records of vesical capacity and pressure were obtained. The first records usually exhibited a greater tonus, as indicated by smaller capacity of the bladder and greater pressure than were shown in records made when the procedure had been repeated a number of



times. The technic used was similar to that employed in making cystometric observations on human beings, except that the subjective sensory experiences were not directly available.

A two-way catheter was introduced into the urinary bladder and a sample of urine preserved for examination. The instrument consists essentially of a water manometer by means of which fluid at room temperature may be pumped from a tank or reservoir at its base into the bladder. This pump is so adjusted that a definite quantity (10 cc.) is delivered with each revolution of a crank which is geared synchronously with a kymograph. As originally described, the inlet connector of the cystometer contained air and communicated with a mercury manometer. In these experiments, for greater accuracy, the air was replaced with water. The outlet connector of the cystometer is attached to one side of the two-way catheter and the inlet connector to the other side. The variations in intra-

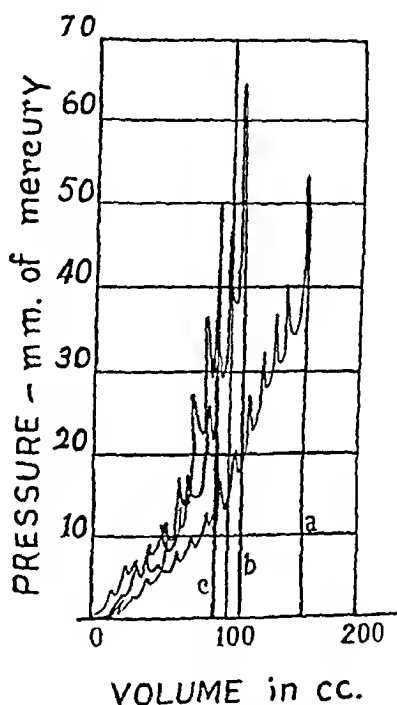


Fig. 2.—Bilateral parasympathetic denervation of the urinary bladder: *a*, pre-operative cystometrogram; *b*, cystometrogram taken twelve days after operation, and *c*, cystometrogram taken thirty days after operation.

cystic pressure are thus recorded on the kymograph by means of a writing point which is attached to a float resting on the mercury column. Strict asepsis was observed during catheterization, and the urine was frequently examined for evidence of urinary infection. The fluid was introduced at a rate of approximately 20 cc. a minute. When the cystometric curves for a particular animal appeared closely similar after repeated observations, the following operative procedures were performed: (1) parasympathetic denervation of the urinary bladder (bilateral), (2) sympathetic denervation of the urinary bladder (bilateral), (3) excision of the hypogastric ganglions on both sides, (4) division of the pudic nerves on both sides and (5) division of the spinal cord at various levels. These operations were done with the animal under ether anesthesia and with strict regard for asepsis. Figure 1 shows the surgical anatomy of the dog in this region. A partial neur-

tomy was done in every instance, and a segment of nerve from 1 to 1.5 cm. in length was excised. Following operation the animals were kept in suitable quarters and fed a uniform diet of dog biscuit and all the water they desired. At varying intervals after operation, cystometric studies were made in the manner previously described. Urinalysis was likewise made frequently. Finally each animal was killed by ether narcosis, and a thorough necropsy was performed.

#### TYPICAL PROTOCOLS OF THE EXPERIMENTS

##### EXPERIMENT 1.—*Bilateral parasympathetic denervation of the urinary bladder.*

The parasympathetic supply of a female dog weighing 11 Kg. was divided by operation on March 19. The course postoperatively was uneventful. Figure 2 shows the cystometric record before and after operation. The postmortem examination, on April 25, gave negative results.

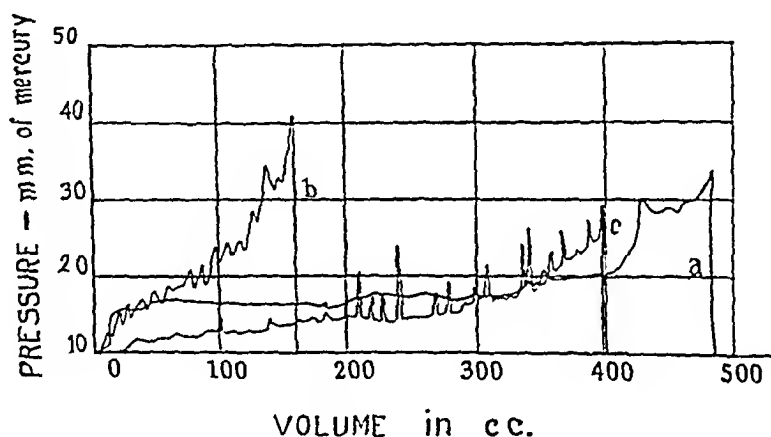


Fig. 3.—Bilateral sympathetic denervation of the urinary bladder: *a*, preoperative cystometrogram; *b*, cystometrogram taken two days after operation, and *c*, cystometrogram taken fifty days after operation.

Curves *b* and *c*, made twelve and thirty days, respectively, after parasympathetic denervation, are apparently normal curves and closely resemble the curves obtained prior to operation. There is nothing in these curves to suggest overbalance of the sympathetic nerves.

##### EXPERIMENT 2.—*Bilateral sympathetic denervation of the urinary bladder.*

On February 16 a sympathetic denervation of the urinary bladder was done on a female dog weighing 17 Kg. The course after operation was without especial event. Figure 3 shows the results of both preoperative and postoperative cystometric studies. The postmortem examination, on April 26, gave normal results.

This dog, a large and docile animal, frequently fell asleep during the cystometric examination. The preoperative cystometrogram, curve *a*, is unusually smooth. Curve *b*, made two days after denervation, was intentionally not completed because of the inflamed condition of the operative wound. The increase in intracystic pressure noted here may be the result of an inflammatory irritation of the abdominal wall rather than the result of parasympathetic overbalance. Curve *c*, made fifty days after operation, is similar to many of the preoperative records.

EXPERIMENT 3.—*Excision of both hypogastric ganglions.*

On February 17 the hypogastric ganglions of both sides were removed from a female dog weighing 15 Kg. The general condition of the animal after operation was good, but unfortunately the urine became infected after the second cystometric examination. Figure 4 shows the cystometric curves obtained. The postmortem examination, on March 30, revealed no abnormalities except moderate cystitis.

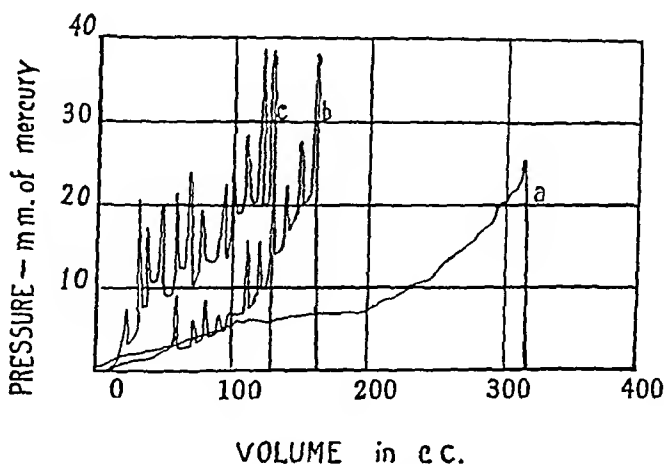


Fig. 4.—Excision of both hypogastric ganglions: *a*, preoperative cystometro-gram; *b*, cystometrogram taken eleven days after operation, and *c*, cystometrogram taken thirty-seven days after operation (cystitis).

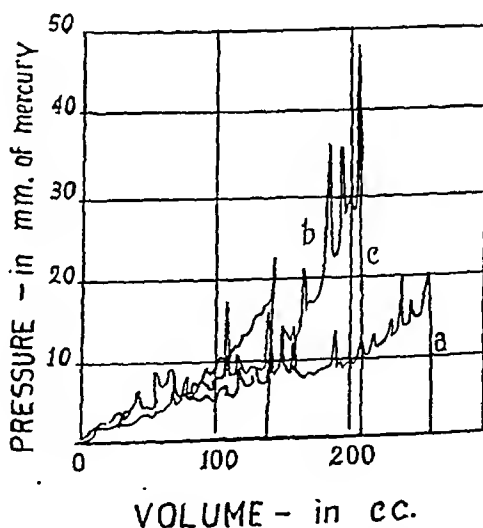


Fig. 5.—Bilateral section of the pudic nerve: *a*, preoperative cystometro-gram; *b*, cystometrogram taken six days after operation, and *c*, cystometrogram taken twenty-one days after operation.

Curve *b* was made on the eleventh day after operation. The urine was free from infection at this time. Curve *c* was made thirty-two days postoperatively. At this time there was marked pyuria. The increase in intracystic pressure and the diminution in capacity are rather striking. If no cystitis was present at the time curve *b* was taken, one might conclude that complete removal of the extrinsic nerve

supply to the bladder is accompanied by definite increase in tonicity of the bladder. In curve *c* the presence of cystitis would be sufficient explanation for the lowered capacity and the increased pressure observed.

EXPERIMENT 4.—*Bilateral section of the pudic nerve.*

On April 13, the pudendal nerves of a female dog weighing 14 Kg. were divided intraperitoneally. The general condition of this animal after operation was excellent. There was neither urinary retention nor infection. The cystometric records are shown in figure 5.

Curve *b*, made six days after operation, shows a reduction in the capacity of the bladder of approximately 50 per cent, but the pressure remained about equal to

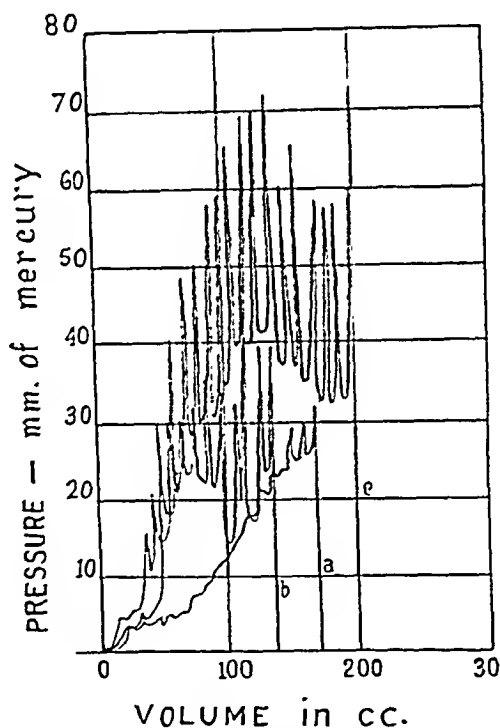


Fig. 6.—Transverse section of the spinal cord between the fourth and fifth lumbar vertebrae: *a*, preoperative cystometrogram; *b*, cystometrogram taken five days after operation, and *c*, cystometrogram taken twelve days after operation.

that noted before operation. Curve *c*, obtained three weeks after operation, shows some increase in the capacity of the bladder and a greater pressure than before. This animal was particularly restless during the cystometric examinations, and there was little uniformity even among preoperative records. Furthermore, there was no urinary infection nor retention of urine. Rose and Rollins<sup>1e</sup> suggested that a physiologic block of the pudic nerve caused by the prolonged pressure of the child's head brought about the condition of postpartum retention. When the pudic nerves, however, were intentionally divided by Learmonth for the relief of pruritis vulvae, no retention of urine occurred, and in one case a normal cystometrogram was obtained.

EXPERIMENT 5.—*Transverse section of the spinal cord caudad to the sympathetic outflow and cephalad to the parasympathetic supply.*

On March 23 a transverse division of the spinal cord at the level of the fourth and fifth lumbar interspaces was done on a female dog weighing 10 Kg. After operation, there were complete paralysis of the hindlegs, urinary retention (from 200 to 250 cc.) and constipation. The urine was normal on the first examination but became infected shortly after operation. Figure 6 shows the cystometric curves obtained. On the twelfth day after operation the animal was killed by ether narcosis. The postmortem examination revealed nothing abnormal except atrophy of the muscles of the hindquarters and severe hemorrhagic cystitis. The upper portion of the urinary tract showed nothing abnormal.

The preservation of the parasympathetic outflow resulted in retention of urine with incontinence, and yet when the bladder was filled a fair degree of tonus remained. Loss of sphincteric control, however, permitted a leakage of fluid from

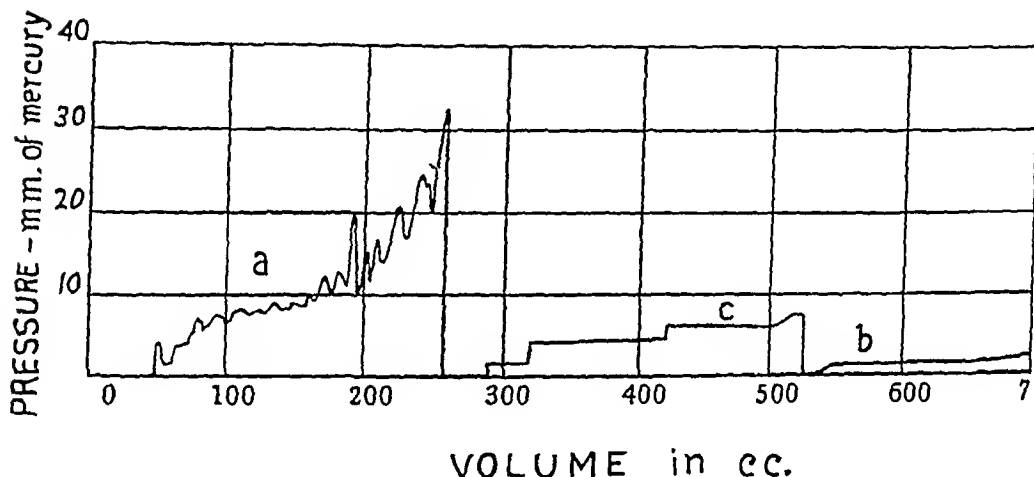


Fig. 7.—A transverse section of the spinal cord between the tenth and the eleventh thoracic vertebra: *a*, preoperative cystometrogram; *b*, cystometrogram taken two days after operation, and *c*, cystometrogram taken eleven days after operation.

the bladder fluid around the catheter. The cystometric curve fell gradually after this occurred. Curve *b* was made five days and curve *c* two days after section of the cord. In curve *c*, despite the cystitis, there is evident increase in both intracystic pressure and capacity. The cause of the extreme notching or toothlike effect of these curves is not entirely clear. It occurs with each ejection of fluid from the pump, but here it was exaggerated far more than in any of the previous experiments.

EXPERIMENT 6.—*Transverse section of the spinal cord cephalad to both the sympathetic and the parasympathetic outflow.*

On March 23, the spinal cord of a female dog weighing 13 Kg. was sectioned transversely between the ninth and the tenth thoracic vertebra. After operation there were paralysis, constipation and urinary incontinence, with marked retention of urine (400 to 500 cc.). The urine on the second examination showed a slight degree of infection. Figure 7 shows the cystometric curves before and after oper-

ation. This animal died on the fifteenth day after operation. At postmortem examination the bladder was markedly contracted, and the mucosa was slightly hemorrhagic. The kidneys, ureter, colon and rectum grossly appeared normal.

In this experiment both the sympathetic and the parasympathetic supply were destroyed. There was a much greater degree of urinary retention and incontinence than in the previous experiment. In curve *b*, made two days after operation, and in curve *c*, made eleven days postoperatively, it will be noted that the capacity of the bladder is tremendously increased, whereas the intracystic pressure is very low. Leakage about the catheter also occurred when the bladder became over-distended. This curve is similar to the cystometrograms obtained clinically in cases of *tabes dorsalis* and of other destructive lesions of the spinal cord in human beings.

EXPERIMENT 7.—Control cystometrograms from a normal dog.

Beginning March 3, a series of cystometrograms were made on a female dog weighing 11 Kg. Figure 8 shows three such curves: (*a*) the first curve made;

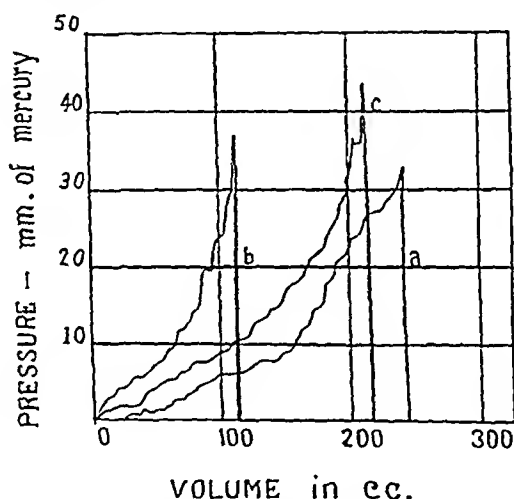


Fig. 8.—Control cystometrograms from a normal dog: *a*, first cystometrogram in the series; *b*, intermediate cystometrogram in the series, and *c*, last cystometrogram in the series.

(*b*) the intermediate curve, and (*c*) the final curve. All the other curves fell within this range. The animal cooperated satisfactorily, and the experiments represent very well the degree of variation which may be expected under normal conditions.

COMMENT

Destructive lesions of the extrinsic nerve supply to the urinary bladder in dogs produced by excising segments 1 to 1.5 cm. in length from the sympathetic, parasympathetic or pudic nerves did not cause appreciable disturbance in the physiology of the bladder. The normal character of cystometric curves was not significantly altered early or late by these procedures. Transverse division of the spinal cord above the lumbar outflow produced the typical picture of "cord bladder" clinically. This condition was readily demonstrated by means of the

cystometer. This evidence tends to support the views previously expressed by McCaughan, Major and Braasch<sup>2</sup> with regard to the value of cystometry clinically and is generally in accord with the results obtained from experimentation with animals by a majority of investigators.<sup>5</sup>

The importance of irritative lesions in producing vesical dysfunction deserves more careful investigation. A practical method for accomplishing prolonged stimulation of nerve tissue in experimental animals has been suggested recently by Loucks<sup>11</sup> and also by Cannon.<sup>12</sup> We have been using a modification of the Cannon technic and propose to demonstrate the effects, if any, of this form of stimulation on the urinary tract, rectum and colon.

#### CONCLUSIONS

The cystometer is of greatest value in demonstrating the effects on the urinary bladder of destructive lesions of the spinal cord. When the lesion was placed elsewhere, as in the extrinsic nerve supply, the cystometric curves were generally normal or of no particular diagnostic aid.

Dr. F. W. Braasch of the Section on Urology at the Mayo Clinic, Rochester, Minn., provided the cystometer used in these experiments.

---

11. Loucks, R. B.: Preliminary Report of a Technique for Stimulation or Destruction of Tissues; Beneath the Integument and the Establishing of Conditioned Reactions with Faradization of the Cerebral Cortex, *J. Comp. Psychol.* **16**:439 (Dec.) 1933.

12. Cannon, Bradford: A Method of Stimulating Autonomic Nerves in the Unanesthetized Cat with Observations on the Motor and Sensory Effects, *Am. J. Physiol.* **105**:366, 1933.

# VASO-ORCHIDOSTOMY WITH INTERPOSED SPERMATOCELE

A PROCEDURE FOR TREATMENT OF STERILITY

SEYMOUR F. WILHELM, M.D.

NEW YORK

The first recorded surgical attempt to reestablish the seminiferous channels was that of Bardenheuer,<sup>1</sup> who in 1886, following excision of the epididymis for tuberculosis, implanted the cut distal end of the vas deferens in the testis. Since then many operations have been devised for the relief of male sterility due to obstructive lesions in the epididymides. These fall into three main categories:

1. Vaso-epididymostomy<sup>2</sup>
2. Vaso-orchidostomy<sup>3</sup>
3. Miscellaneous operations
  - (a) Vaso-orchidocystostomy<sup>4</sup>
  - (b) Sac epididymostomy<sup>5</sup>

---

From the Surgical Services of the Beth Israel and the Montefiore Hospitals.

1. Bardenheuer, B.: Die operative Behandlung der Hodentuberculose durch Resection des Nebenhodens, *Mitt. a. d. Köln. Bürgerhospital* 3:129, 1886.

2. (a) Bogoljuboff, W.: Experimentelle Untersuchungen über die Anastomosenbildung an den ableitenden Samenwegen, *Arch. f. klin. Chir.* 72:449, 1904. (b) Hagner, F.: Anastomosis of Vas Deferens to Epididymis, *Tr. Am. A. Genito-Urin. Surgeons* 8:142, 1913; (c) Sterility in the Male, *J. Urol.* 13:377, 1925; (d) Sterility in the Male, *Surg., Gynec. & Obst.* 52:330, 1931. (e) Lespinasse, V. D.: Obstructive Sterility in the Male, *J. A. M. A.* 70:448 (Feb. 16) 1918. (f) Martin, E.; Carnett; Levi, and Pennington: *Pennsylvania M. Bull.* 20:388, 1902; (g) Sterility from Obstruction at the Epididymis Cured by Operative Means, *New York M. J.* 78:697, 1903.

3. (a) Rasumowsky, W. J.: Eine neue Operation am Hoden, *Arch. f. klin. Chir.* 65:2, 1902. (b) Rolnick, H. C.: An Operation for Sterility in the Male, *Surg., Gynec. & Obst.* 45:557, 1927. (c) Stutzin, J. J.: Vaso-orchidostomie, *Ztschr. f. Urol.* 18:132, 1924; (d) Zur Frage der Vaso-orchidostomie, *Zentralbl. f. Chir.* 53:264, 1926. Bardenheuer.<sup>1</sup>

4. (a) Gara, M.: Ueber Cysten und Hohlrumbildungen, *Zentralbl. f. Chir.* 52:2238, 1925. (b) Lichtenstern, R., and Gara, M.: Vaso-orchidostomie, *Ztschr. f. urol. Chir.* 24:156, 1928.

5. Lespinasse, V. D.: (a) The Relief of Sterility by Means of Permanent Epididymostomy, *J. A. M. A.* 63:1916 (Nov. 28) 1914; (b) *Tr. A. Genito-Urin. Surgeons* 12:339, 1919; (c) Sterility in the Male, *Illinois M. J.* 61:509, 1932.



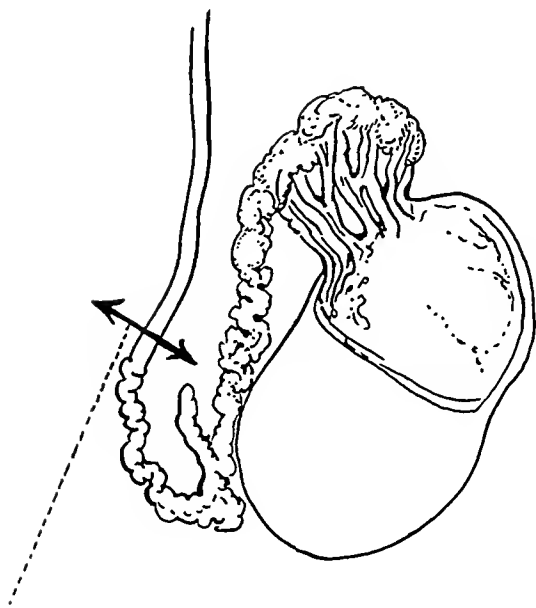


Fig. 1.—The first stage in the operation, permanent vasostomy, in which the vas deferens is cut.

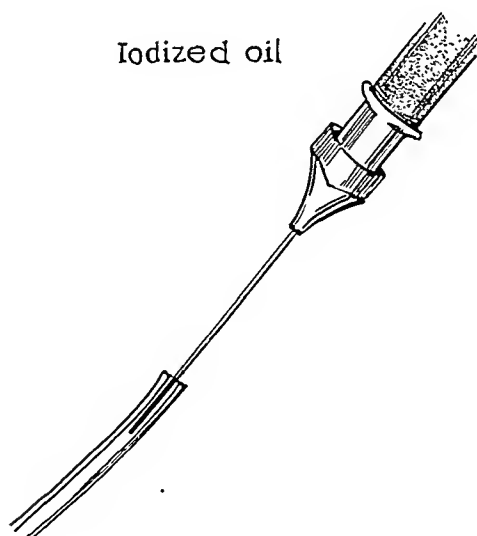


Fig. 2.—A step in the first stage showing a blunt needle inserted into the vas deferens for the injection of iodized oil for seminal vesiculography.

(c) Transplantation of the saphenous vein as a substitute for the vas deferens<sup>6</sup>

(d) Vaso-urethrostomy<sup>7</sup>

There are valid objections to most of these operations on anatomic and physiologic grounds.<sup>8</sup>

It appears from a review of the literature that Martin's vaso-epididymostomy with technical modifications is the most popular and the most successful operation for the reestablishment of the seminiferous channels following bilateral obstructive epididymitis. The

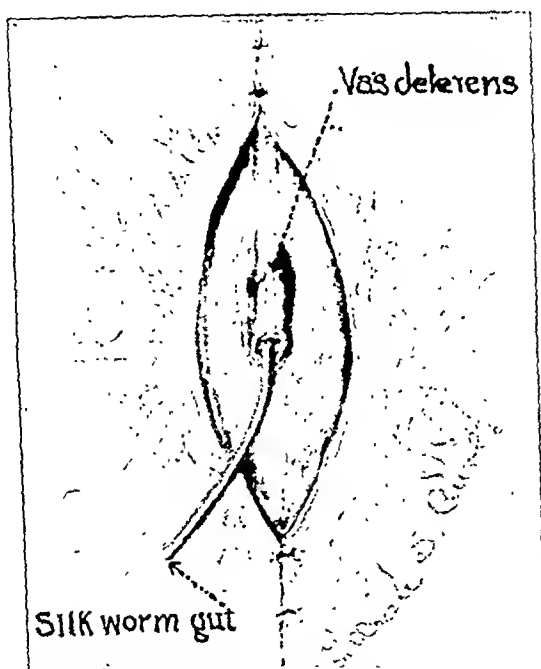


Fig. 3.—The first stage completed. Note that the skin is loosely sutured about the vasostomy opening, leaving a raw surface for epithelization. Scrotal hair, though shaved at the time of the operation, has been diagrammatically inserted.

largest series of cases has been reported by Hagner.<sup>2d</sup> He achieved successful results in nineteen of thirty-one patients, or 61 per cent. However, this operation has been successful in the hands of only a few surgeons and has never attained widespread popularity. The large number of unreported failures is undoubtedly the reason for the pessi-

6. von Mezö, A.: Neue Richtungen in der Behandlung des mechanischen Aspermatisms, *Ztschr. f. urol. Chir.* 21:33, 1926.

7. Boari, A.: L'implantation des canaux déferents dans l'urèthre antérieur, *Semaine méd.* 29:445, 1909.

8. Lichtenstern and Gara.<sup>4b</sup> Rolnick.<sup>3b</sup>

mistic outlook toward this relatively nondangerous operation for an otherwise hopeless condition.

On the other hand, it is agreed that the likelihood of success is greatly enhanced if a spermatocele is present or can be formed artificially.<sup>9</sup> Lespinasse,<sup>5a</sup> Rolnick<sup>10</sup> and Lichtenstern and Gara<sup>4b</sup> have worked toward this end, with, however, limited or no success. It would seem that the solution of this problem, i. e., the artificial creation

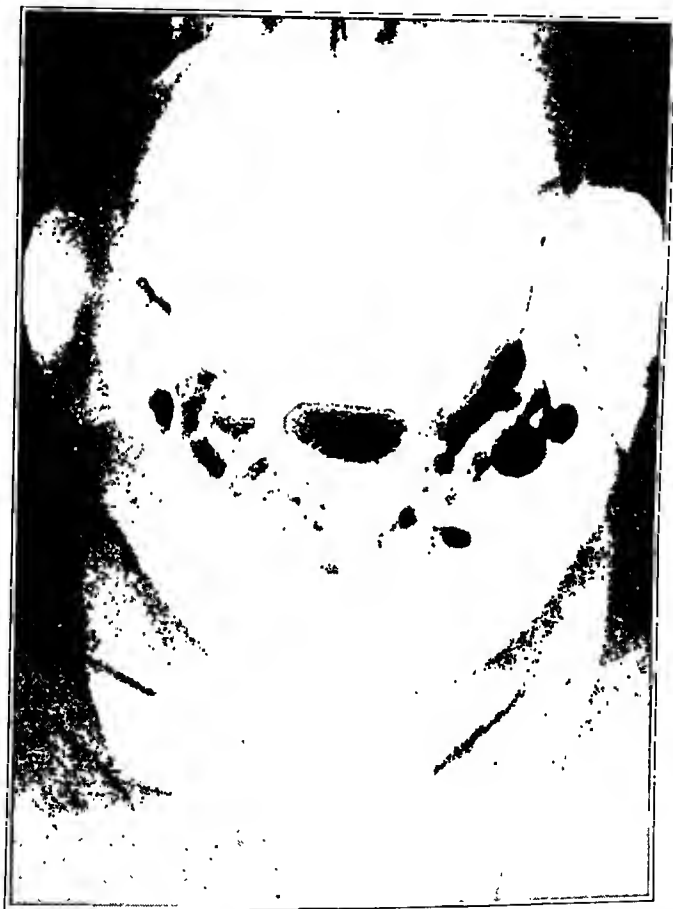


Fig. 4.—A vasoseminal vesiculogram demonstrating the patency of both vasa deferentia. The seminal vesicles are normal. Note the iodized oil in the bladder.

of a spermatocele, would materially increase the percentage of success of operations to reestablish the seminiferous channels. With this in mind I have attempted to devise an operative procedure which would more nearly reproduce the normal anatomic conditions.

The criteria for this operation were as follows: 1. The entire spermatogenic tissue should be used. 2. The testis should not be

9. Hagner.<sup>2d</sup> Rolnick.<sup>3b</sup>

10. Rolnick, H. C.: The Etiology of Spermatocele, *J. Urol.* **19**:613, 1928.

damaged. 3. The site of the anastomosis should be completely epithelial so that a minimum of scar was formed. 4. A funnel-shaped sac lined with epithelium, analogous to a spermatocele, should be established to unite the larger cut open surface of the tubules of the epididymis or of the rete testis to the smaller divided end of the vas deferens.

Following experiments on animals in the pathologic laboratories of the Montefiore Hospital, this operation for the reestablishment of the seminiferous channels was carried out in two stages. The first stage

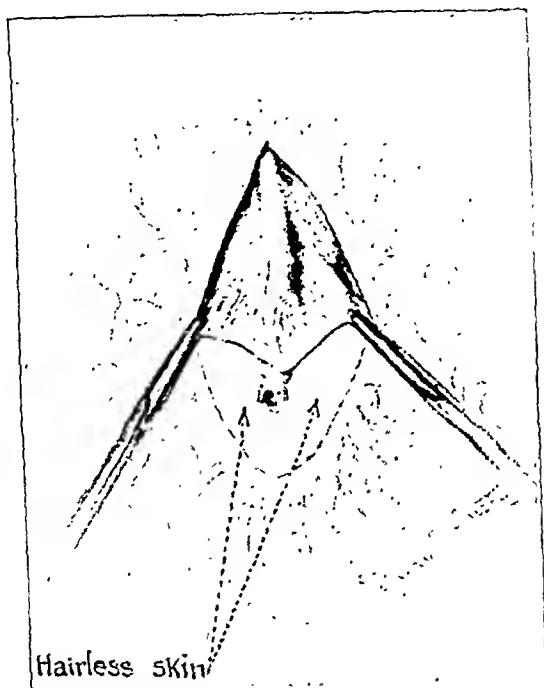


Fig. 5.—The second stage in the operation, vasosac orchidostomy. The vas deferens is freed with an attached cuff of new hairless skin.

consisted of permanent vasostomy. After complete healing had taken place the second stage, vasosac orchidostomy, was performed.

#### TECHNIC OF THE OPERATION

*First Stage: Permanent Vasostomy.*—The vas deferens is isolated through a small high scrotal cutaneous incision. Vaso seminal vesiculography is then performed by the injection of iodized oil into the distal portion of the vas deferens to demonstrate its patency into the urethra (figs. 1, 2 and 4).

The vas is cut across close to the epididymis, and its distal end implanted into the scrotal skin, creating a permanent vasostomy. A strand of silkworm gut is left in the lumen of the vas deferens. It is very important that the scrotal skin be loosely sutured around the implanted end of the vas deferens, leaving a raw

area. This allows a cuff of new hairless epithelium to grow inward from the edges of the scrotal wound to and surrounding the vasostomy opening (fig. 3).

*Second Stage: Vasosac Orchidostomy.*—The testis and epididymis are exposed through a low scrotal incision. The epididymis is aspirated or incised for spermatozoa; the testis can be aspirated if necessary. The epididymis is incised freely or cut across at the place where spermatozoa are found. If no spermatozoa are found in the epididymis, an epididymectomy is performed, cutting transversely across the efferent ducts of the rete testis, leaving them gaping widely open (fig. 6 *A*). Bleeding is carefully controlled, preferably by pressure and the application of epinephrine. The vas deferens is freed with a cuff of hairless skin remaining attached around the vasostomy opening (fig. 5). The edges of the cutaneous cuff are sutured to the cut margins of the epididymis or to the tunica albuginea around but at some distance from the sectioned efferent ducts of the rete testis, forming an umbrella-like sac (fig. 6). The incision of scrotal skin is closed with interrupted plain catgut sutures without drainage.

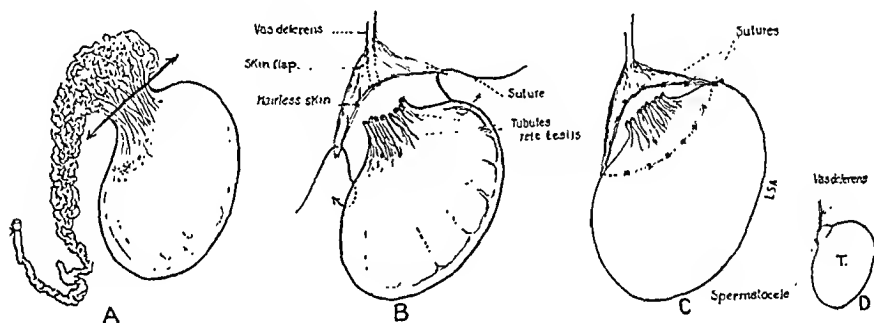


Fig. 6.—A diagram of the steps in the vasosac orchidostomy. *A* indicates the stage at which the epididymis is cut, *B* and *C*, the skin flap with the end sutures, and *D*, the external view of the completed operation.

#### COMMENT

By performing the operation in two stages, i. e., with preliminary vasostomy, one can be fairly certain that the opening of the vas deferens is patent before proceeding with the major step of the anastomosis. This tends to eliminate late stricture and occlusion of the vas deferens at the site of anastomosis, a frequent cause of failure of these operations.<sup>3b</sup> If for some reason the vasostomy opening should close, another can easily be made.

In addition, the presence of an umbrella-like cuff of hairless new skin epithelium about the vas deferens (figs. 5 and 6) enables one to place the sutures a good distance away from the site of anastomosis. Thus there is no irritation or inflammation by foreign bodies near the opening of the epididymal tubules or the efferent ducts of the rete testis. This makes the operation quite simple for surgeons of ordinary skill and eliminates another cause of failure of vaso-epididymostomy.

i. e., inflammation and necrosis about the suture line with later scar contracture closing the anastomosis opening.<sup>11</sup>

Though Lespinasse in 1916<sup>5a</sup> proposed the formation of a spermatic sac or spermatocele of vein, skin or bladder mucosa, there is no report of such a procedure ever having been carried out. Unfortunately Lespinasse did not consider the possibility of implanting the vas deferens into such an artificially created spermatic sac but confined its application to cases in which the pelvic vas deferens was occluded. He suggested periodic tapping of the sac for purposes of artificial insemination. Another obstacle to the ultimate success of his procedure was the use of Delbet's rubber instead of living epithelial tissue to form the sac. So far as can be ascertained from the literature, skin has never before been used to create an artificial spermatocele or spermatic sac into which the vas deferens has been implanted. In addition, no mention has been found of the application of vasoseminal vesiculography for the purpose of proving patency of the seminiferous system from the site of anastomosis of the vas deferens into the urethra.

The experimental work and clinical experiences on which this technic is founded will be reported in a later communication.

---

11. Rolnick,<sup>2b</sup> Stutzin.<sup>2d</sup>

# MELANOSIS COLI

## ITS CLINICAL SIGNIFICANCE

ALFRED J. ZOBEL, M.D.

AND

DAVID A. SUSNOW, M.D.

SAN FRANCISCO

Since its first description by Cruveilhier<sup>1</sup> in 1829 melanotic pigmentation of the large intestine had been only occasionally observed. From his autopsy observations made in 1858, Virchow<sup>2</sup> applied the term melanosis coli to the condition. It was 1911 before the first clinical report by Pick<sup>3</sup> appeared on the recognition sigmoidoscopically of this discoloration of the intestine.

While melanosis coli is not a rare condition it is practically unknown to the average physician. When observed sigmoidoscopically it usually has been passed by or referred to casually as "brown bowel" or by some other descriptive term and its clinical significance overlooked. The latter circumstance has prompted us to present this paper.

### GROSS APPEARANCE THROUGH THE SIGMOIDOSCOPE

The mucosal pigmentation in melanosis coli varies widely in different persons. It is usually some shade of brown ranging from a light, almost gray, tone to a deep, dark hue almost inky black. In the earliest stages the pigmentation is demonstrable only microscopically. Most writers have described the pigmentation as being deepest in the cecum and ascending colon and becoming gradually less pronounced distally and rarely being more intense in the distal part of the intestine. The entire colon usually is not involved.

According to Lubarsch and Borchardt,<sup>4</sup> the pigmentation is mainly in the cecum, appendix and ascending colon. Lignac<sup>5</sup> stated that the

---

From the Department of Proctology, Division of Surgery, of the Mount Zion Hospital.

1. Cruveilhier, J.: *Anatomie pathologique du corps humain*, Paris, J.-B. Baillière, 1829-1835, vol. 19, p. 6.

2. Virchow, Rudolf: *Die pathologischen Pigmente*, Virchows Arch. f. path. Anat. **1**:379, 1847.

3. Pick, L.: *Ueber die Melanose der Dickdarmschleimhaut*, Berl. klin. Wchnschr. **48**:840 (May 8); 884 (May 15) 1911.

4. Lubarsch, O., and Borchardt, H.: *Die Melanosis Coli*, in Henke, F., and Lubarsch, O.: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1929, vol. 4, p. 75.

5. Lignac, G. O. E.: *Ueber sogenannte "Melanosis Coli," Krankheitsforschung* **2**:162, 1926.

melanosis is mainly in the cecum and rectum, with occasional pigmentation in the ileum. Stewart and Hickman<sup>6</sup> reported that the discoloration is almost invariably more intense in the cecum and ascending colon, although rarely the melanosis may be deeper in the distal than in the proximal portion of the large intestine. Bockus<sup>7</sup> and his co-workers found that when the pigmentation is not uniformly distributed it is always more intense in the rectum and in many cases gradually diminishes in the upper portion of the descending intestine.

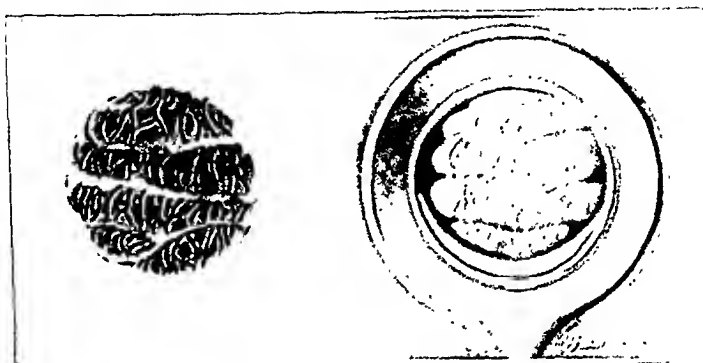


Fig. 1.—A sketch showing the common form of melanosis coli.

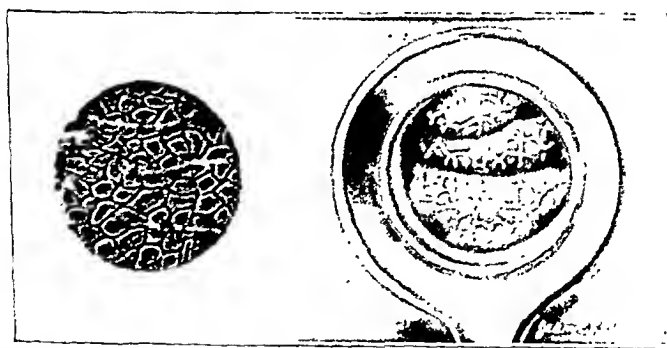


Fig. 2.—A sketch showing the crocodile hide type of melanosis coli.

Other than a melanotic discoloration there are usually no changes in the mucosa of the intestine. Frequently there is accompanying mucous colitis. There are no indications of pigmentation elsewhere, although metastasis of the pigment to the mesocolic lymph nodes occurs at times. There is no evidence as yet as to the more widespread

6. Stewart, M. J., and Hickman, E. M.: Observations on Melanosis Coli, *J. Path. & Bact.* **34**:61, 1931.

7. Bockus, H. L.; Willard, J. H., and Bank, Joseph: Melanosis Coli: The Etiologic Significance of the Anthracene Laxatives, *J. A. M. A.* **101**:1 (July 1) 1933.



metastasis of melanosis. The pigmented area of the portion of the intestine affected is broken up into small polyhedral shape by a network of fine unpigmented lines which correspond, according to Pick, to the ramifications of the mucosal blood vessels. In less advanced stages the pigmented areas are smaller as well as lighter, with a brownish stippling against a normal-appearing mucosal background. The solitary follicles of the intestine, being devoid of pigment, stand out as small yellow follicles the size of a pinhead. They are marked even in the early stages of melanosis and are helpful in making macroscopic diagnosis.

The appearance of the mucosa of the intestine has been compared to that of snake skin, crocodile hide, tiger skin and a cross-section of nutmeg.

#### HISTOLOGIC APPEARANCE

The pigmentation is usually confined to the stroma of the mucous membrane, where it lies in the cytoplasm of large mononuclear cells, the exact nature of which has not been settled. The distribution in the mucosa varies. In mild cases it is usually in the mucosal villi, while in the advanced stage it is either in the depths of the mucosa close to the muscularis mucosae or scattered throughout its thickness. This distribution is probably due to the formation of melanin superficially followed by a migration downward.

The pigment is usually intracellular, but free granules are also present. The epithelium of the mucosa is usually pigment-free.

#### CHARACTER AND SOURCE OF THE PIGMENTATION

There is a great diversity of opinion with regard to the character and source of the pigmentation in melanosis coli. It is generally believed that the pigment is a true melanin or melanin-like substance. It was formerly believed that pigmentation of the intestine was due to ingestion of preparations of heavy metals, such as mercury or lead. This view, however, was not substantiated by subsequent chemical analysis of sections of pigmented melanotic intestines. From his chemical studies, Virchow suggested a hematogenous origin. This view was put forth by others, and the condition is still referred to in many places in the literature as hemochromatosis (Lynch<sup>8</sup>; Gant<sup>9</sup>). It is difficult to explain the limitation of the pigmentation to the colon if the source is hematogenous.

8. Lynch, J. M.: *Diseases of the Rectum and Colon*, Philadelphia, Lea & Febiger, 1914, p. 374.

9. Gant, S. G.: *Diseases of the Rectum, Anus and Colon*, Philadelphia, W. B. Saunders Company, 1923, p. 86.

Vascular congestion with a predisposition to the formation of pigment (Solger<sup>10</sup>), hemorrhage into the intestine with subsequent bacterial action (Lignac<sup>5</sup>) and disturbance of the chromogenic function of the liver (Lynch<sup>6</sup>) have been advanced as probable causes of melanosis coli.

According to Pick, the aromatic products of protein disintegration of the contents of the intestine (indole, skatole) are absorbed from the



Fig. 3.—A high power photomicrograph showing pigmentation in the stroma of the mucous membrane of the rectum.

intestine and converted into melanin within the connective tissue cells of the mucosa by the action of a tyrosinase-like ferment produced by the connective tissue cells. This ferment is produced only in certain persons. Other theories propose the formation of a ferment in the

10. Solger, F. B.: Dickdarmmelanose, Inaug. Dissert., Greifswald, 1898; quoted by Lubarsch and Borchardt.<sup>4</sup>

contents of the intestine and the production of melanin by that portion of the mucosa which comes in contact with the ferment (McFarland<sup>11</sup>), the production of pigment by bacterial action (Dalldorf<sup>12</sup>) and the derivation of melanin from foodstuffs and then phagocytosis by the cells of the mucosa of the intestine (Laidlaw<sup>13</sup>).

The etiologic significance of the anthracene laxatives in relation to melanosis coli has recently been described by Bockus and his co-workers.<sup>7</sup> These observers concluded that "the anthracene laxatives either contain or elaborate a pigment within the bowel which is phagocytised by the deep mucosal cells causing melanosis coli." They obtained a history of the long use of anthracene laxatives, usually cascara sagrada, in 100 per cent of their cases of melanosis of the bowel. The association of melanosis with constipation or stasis seems

*Clinical Features in Patients with Melanosis of the Bowel*

Patient	Sex	Age, Years	Chief Complaint	Appearance of Mucosa	Laxative Taken	Other Observations
1	M	56	Mucous discharge from rectum	Scattered pigmented points	Cascara sagrada	Mucous colitis
2	F	50	Bleeding by rectum	Alligator skin	Cascara sagrada	Mucous colitis
3	M	69	Pain in rectum	Alligator skin	Aloe, strychnine and phenolphthalein*	Proctitis; internal hemorrhoids
4	F	52	Bleeding by rectum	Tiger skin	Cascara sagrada	Internal hemorrhoids
5	F	40	Constipation	Alligator skin	Cascara sagrada	Internal hemorrhoids; mucous colitis
6	M	64	Bleeding by rectum	Alligator skin	Cascara sagrada	Internal hemorrhoids
7	F	41	Pain in rectum	Alligator skin	Cascara sagrada	Fissure in the anus

\* Aloe contains an anthracene derivative.

to be definitely established. This probably explains the frequency of melanosis in surgically resected appendixes and in malignant processes of the intestine.

REPORT OF CASES

In 7 of 200 persons examined by sigmoidoscope in our clinic we observed melanotic discoloration of the bowel. This was an incidence of 3.5 per cent. In five the appearance could be likened to an alligator skin. Another suggested somewhat the cross-section of nutmeg and the other presented widely separated stipplings of light brown pigmentation. The table summarizes certain clinical features of our cases.

11. McFarland, W. L.: Pigmentation of the Hind-Gut, J. A. M. A. **69**:1946 (Dec. 8) 1917.

12. Dalldorf, G. J. G.: Melanosis Coli, Beitr. z. path. Anat. u. z. allg. Path. **78**:225 (Aug.) 1927.

13. Laidlaw, G. F.: Melanoma Studies, Am. J. Path. **8**:447 (Sept.) 1932.

The most striking feature was that all these seven patients took cascara sagrada. This is quite in agreement with the report of Bockus and his co-workers. It is of interest that when one of our patients was told that she had "brown bowel" she suggested that it might be due to the cascara sagrada which she had been taking for a long time, "for cascara is brown."

In all our cases constipation had been present for many years. Examination disclosed intestinal stasis in each. The headache, drowsiness, dizziness and other symptoms of which these patients complained were probably due to the colonic stasis and not to the melanosis, for similar symptoms may occur in patients with stasis of the colon without melanosis. It is our belief that melanosis coli per se produces no symptoms. We have no evidence that this pigmentation of the bowel is detrimental.

Contrary to the report of most observers that the pigmentation is deepest in the cecum and ascending colon and becomes more intense in the distal part of the intestine, we found that the pigmentation was deepest distally, in the rectum just inside the anal sphincter. Above this area of deepest pigmentation the coloration became gradually lighter as far as we could determine sigmoidoscopically.

Bockus reported that from four to twelve months is usually necessary for a complete disappearance of the pigmentation when proper treatment is instituted. We have observed that following treatment for the constipation and usually associated catarrhal colitis there was a partial clearing up of the pigmentation. Our treatment consisted of nonanthracene cathartics, enemas of tap water, and a nonputrefactive diet. We have not observed a complete disappearance. Our first patient has been under observation and treatment for one and one-half years.

#### SUMMARY

The gross and histologic characteristics of melanosis coli have been reviewed.

Melanosis coli was observed in seven of two hundred consecutive persons who underwent sigmoidoscopic examinations.

The chief apparent factors were chronic constipation and the use of anthracene laxatives over a long period of time.

The pigmentation partially disappears when the anthracene laxatives are stopped and steps are taken for the correction of the constipation.

Melanosis coli per se is not detrimental.

# GANGRENE OF THE BUTTOCK, PERINEUM AND SCROTUM DUE TO ENDAMOEBA HISTOLYTICA

REPORT OF A CASE

FRANK L. MELENEY, M.D.

NEW YORK

AND

HENRY E. MELENEY, M.D.

NASHVILLE, TENN.

In a recent paper one of us (F. L. M.)<sup>1</sup> presented a clinical and bacteriologic differential diagnosis between certain varieties of acute and chronic infectious gangrene of the skin. One of the chronic forms which was described in that summary was attributed to the pathogenic action of *Endamoeba histolytica*, but it was pointed out that in the reports of cases which had appeared in the literature no mention had been made of a careful study of the anaerobic organisms present in the lesion and that in many cases the identification of the protozoon present as *E. histolytica* was open to question. In certain of the cases, to be sure, there was direct evidence and in others circumstantial evidence that *E. histolytica* was present and was playing a prominent, if not a predominant, rôle in the production and continuation of the disease process.

Recently we have had the opportunity of observing and treating a patient in whose lesion we were able not only to identify *E. histolytica*, apparently actively engaged in a destructive process in the periphery of the affected area, but to rule out by careful anaerobic studies the presence and activity of any anaerobic or micro-aerophilic organisms such as are found constantly in certain other forms of chronic gangrene with which this disease might be confused. We have also been able to observe certain clinical characteristics of this disease which might be helpful in differentiating it clinically from some of the other types of infectious gangrene of the skin. For these reasons it seems worth while to report our observations.

---

From the Surgical Service of the Presbyterian Hospital, New York, and the Department of Preventive Medicine and Public Health, Vanderbilt University School of Medicine, Nashville, Tenn.

1. Meleney, F. L.: A Differential Diagnosis Between Certain Types of Infectious Gangrene of the Skin, Surg., Gynec. & Obst. 56:847, 1933.

## LITERATURE

Amebiasis is generally believed to be a tropical disease, yet it frequently occurs sporadically throughout the temperate zones, and the recent experience in Chicago indicates that it may reach epidemic proportions in northern climates.<sup>2</sup> Amebic infection of the skin has usually been described as occurring after the spontaneous or surgical drainage of a deep focus of amebic infection, such as an abscess in the liver or a peritoneal abscess following a perforated ulcer of the colon. Such cases have been reported by Heimbürger,<sup>3</sup> Nasse,<sup>4</sup> Daborn and Heymann,<sup>5</sup> Heymann and Ricou,<sup>6</sup> Gauducheau,<sup>7</sup> Carmini,<sup>8</sup> Ch'eng,<sup>9</sup> M. F. Engman Jr. and H. E. Meleney,<sup>10</sup> Cole and Heideman,<sup>11</sup> Marwits and Van Steenis<sup>12</sup> and others. Maxwell<sup>13</sup> and Van Hoof<sup>14</sup> described fistulas, abscesses and ulcers in the region of the anus and buttocks which they attributed to the ameba. M. F. Engman Sr. and Heithaus<sup>15</sup> and Hansen and Stark<sup>16</sup> described lesions of the skin which were not associated with

2. Bundesen, H. N.; Tonney, F. O., and Rawlings, I. D.: The Outbreak of Amebiasis in Chicago During 1933: Sequence of Events, *J. A. M. A.* **102**:367 (Feb. 3) 1934; Amebiasis Outbreak in Chicago: Report of a Special Committee, *ibid.* **102**:369 (Feb. 3) 1934.

3. Heimbürger, L. F.: Amebiasis Cutis, with a Survey of the Medical Literature to Date, *Arch. Dermat. & Syph.* **11**:49 (Jan.) 1925.

4. Nasse, D.: Ueber einen Amöbenbefund bei Leberabscessen, Dysenterie und nosocomial Gangrän, *Arch. f. klin. Chir.* **43**:40, 1892.

5. Daborn and Heymann: Abscès amibien du foie, suivi de phagédénisme de la plaie opératoire et d'abcès cutané amibien, *Bull. Soc. méd.-chir. de l'Indo-Chine* **3**:518, 1912.

6. Heymann and Ricou: Un cas de phagédénisme cutané amibien, *Bull. Soc. méd.-chir. de l'Indo-Chine* **7**:64, 1916.

7. Gauducheau: A propos de l'ulcère phagédénique amibien, *Bull. Soc. méd.-chir. de l'Indo-Chine* **7**:118, 1916.

8. Carmini, A.: Phagédénisme cutané amibien, *Bull. Soc. path. exot.* **5**:216 and 799, 1912.

9. Ch'eng, C. C.: Cutaneous Amoebiasis Resulting from Ruptured Liver Abscess Coincident with Kala Azar: Report of Case, *China M. J.* **45**:350, 1931.

10. Engman, M. F., Jr., and Meleney, H. E.: Amebiasis Cutis (*Endameba Histolytica*): Report of Two Cases, *Arch. Dermat. & Syph.* **24**:1 (July) 1931.

11. Cole, W. H., and Heideman, M. L.: Amebic Ulcer of Abdominal Wall Following Appendectomy with Drainage: Report of a Case, *J. A. M. A.* **92**:537 (Feb. 16) 1929.

12. Marwits, E. L., and Van Steenis, P. B.: A Case of Amebiasis Cutis After Incision of Periceal Abscess, *Urol. & Cutan. Rev.* **35**:313, 1931.

13. Maxwell, J. L.: Fistulous Diseases of the Buttocks, *Tr. Roy. Soc. Trop. Med. & Hyg.* **6**:50, 1912.

14. Van Hoof, L.: Abscès, fistules et ulcères, d'origine amibienne, *Ann. Soc. belge de méd. trop.* **6**:45, 1926.

15. Engman, M. F., and Heithaus, A. S.: Amebiasis Cutis, *J. Cutan. Dis.* **37**:715, 1919.

16. Hansen, G. M., and Stark, L.: Amebiasis Cutis with Report of Case, *Nebraska M. J.* **16**:23, 1931.

an internal amebic disease and which were thought to be infected with amebas introduced from without.

Ngai and Frazier<sup>17</sup> recently reported three cases of a condition which apparently falls into the group of cutaneous amebiasis. Their first patient suffered from a perianal condylomatous lesion with a punched-out ulceration which gradually increased in size for three weeks. This was preceded by a period of bloody diarrhea lasting for three weeks. On his admission to the hospital an examination for amebas in the stools gave negative results, and no spirochetes could be found in the lesion. Cultures yielded a nonhemolytic streptococcus and an unidentified gram-positive bacillus. Anaerobic cultures were not reported. The lesion failed to respond to local nonspecific treatment. Two weeks after the patient's admission a scraping from the wall of the ulcer was examined and *E. histolytica* was found. Its presence in the tissue was confirmed by biopsy. The lesion promptly healed after the administration of emetine hydrochloride hypodermically and chiniofon locally. There seems to be no doubt that the amebas were active in the pathologic process and were probably responsible for it. The second patient had a syphilitic lesion of the urethra secondarily contaminated by amebas. The third patient had a papilloma of the anus secondarily invaded by amebas. The authors were not sure that the amebas were of primary importance in the last two cases. Their report contained a good review of the literature.

#### REPORT OF CASE

*History.*—S. J. W., a Chinese kitchen helper, aged 51, was admitted to the Emergency Clinic of the Presbyterian Hospital on Dec. 22, 1933. He spoke no English, and his "interpreter" was not able to give a detailed history or to answer questions except to say that the patient was known to have had diabetes for several years. The man was obviously desperately ill.

On the second day we were able to obtain the following fragmentary notes: Eight years before admission he was found to have diabetes. Under treatment by a physician he was rendered sugar-free. He had taken insulin from time to time, but none recently. During the previous two years he had lost from 40 to 50 pounds (18.1 to 22.7 Kg.) and had had periods of bloody diarrhea which came on every two or three months and lasted for about two weeks. There was no associated abdominal or rectal pain with these attacks of bleeding, and he had received no medication for them. One month before admission he noticed a small, hard, tender lump just to the right of the anus. This gradually increased in size and tenderness for three weeks until he could not sit down or defecate without pain. About ten days before admission the whole area "burst" and discharged large quantities of foul-smelling pus and necrotic tissue. Since that time he had steadily gone down hill.

---

17. Ngai, S. K., and Frazier, C. N.: Cutaneous Amoebiasis: A Review and a Report of Three Cases Observed in North China, *Chinese M. J.* 47:1154, 1933.

*Examination.*—The patient was dehydrated and had an acetone breath, and the lesion filled the surrounding atmosphere with a foul, cadaveric odor. His skin was extremely pale and sallow. His teeth were carious, and his throat was dry. Examination of the lungs revealed fine crackles at both apexes; otherwise they were clear. The heart was not enlarged, the sounds were of fair quality, and there was a systolic murmur at the apex. The abdomen was soft and symmetrical and was not tender. On the right buttock there was a large foul-smelling ulceration extending from the upper margin of the sacrum down to the upper third of the thigh, outward to the great trochanter of the femur and inward to the anal region, along the whole length of the intergluteal fold forward to the perineum and upward in the right groin. In the upper portion the margin was irregular with rolled-in skin and moderate undermining. The region of the anus was completely undermined with a crenated margin of skin and a puckered cutaneous surface. Extending outward from the anus was an irregular area of skin with rolled-in margins and a corrugated surface. Near the anus was a hard fibrous

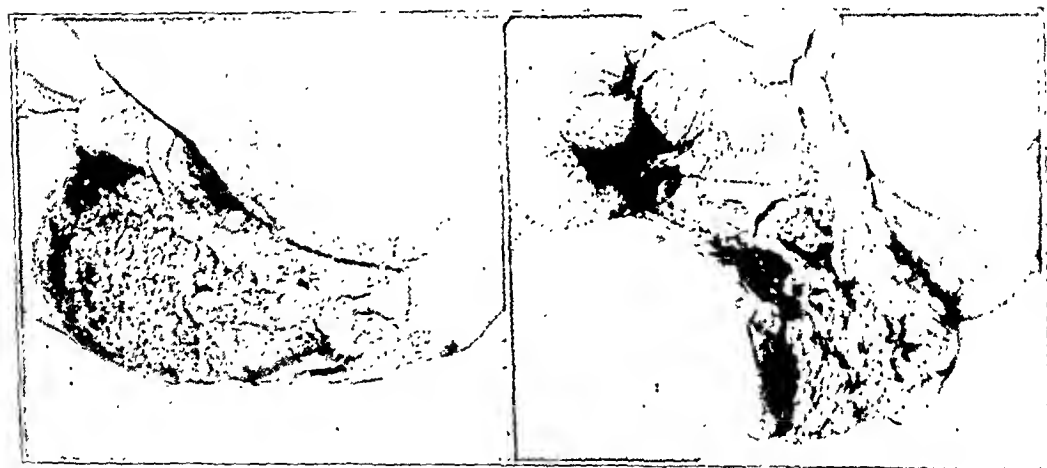


Fig. 1.—The lesion at the time of the patient's admission to the hospital. Note the undermined skin with its wrinkled surface and the zone of gangrene below, sharply demarcated from the living skin which is not raised. The base of the ulcer is shaggy.

nodule. At the lower margin of the lesion on the thigh and in the region extending upward in the right groin was a strip of gangrenous skin firmly adherent to the margin of living skin and fairly sharply demarcated from it. The gangrenous skin was depressed, but the living skin was not raised or purplish and there was no blush outside the area of gangrene. The lower margin of the scrotum on the right side was also undermined, and the right margin of the scrotum was gangrenous. The base of the ulcer consisted of very shaggy dusky granulation tissue covered with a foul-smelling grayish exudate (fig. 1). The patient's temperature was 101 F., the pulse rate, 100, the respiratory rate, 20, and the blood pressure 110 systolic and 70 diastolic. Analysis of the blood revealed: hemoglobin content, 25 per cent; red blood cells, 2,120,000, and white blood cells, 14,000, with polymorphonuclears, 87 per cent. The urine showed sugar (4+), acetone (4+) and diacetic acid (4+). The sugar content of the blood was 269 mg. per hundred cubic centimeters, and the carbon dioxide combining power, 49 cc. per hundred cubic centimeters.



*Course.*—The patient required emergency treatment to reduce the acidosis, lower the blood sugar, increase the body fluids and raise the hemoglobin content. It was thought that any operative procedure at that time would prove fatal. He was given 30 units of insulin at once, and 1,500 cc. of solution of sodium chloride by hypodermoclysis and 1,500 cc. intravenously. Orange juice (120 cc.) was given by mouth every hour. Each specimen of urine was tested for sugar, acetone and diacetic acid, and 10 units of insulin was given following a strongly positive test for sugar and 5 units after a weakly positive test. The patient improved at once and the next day he was given a fluid diet with 150 Gm. carbohydrate, 70 Gm. protein and 100 Gm. fat with insulin in three doses during the day of 15, 10 and 10 units. He was then given a transfusion of blood, and his condition steadily improved.

*Diagnosis.*—The history suggested the possibility of an amebic infection, and an intern made an examination of the exudate from the wound for amebas, but none were found. Examination of the stool for amebas was ordered, but through a misunderstanding it was not made at this time. A bit of tissue sent to the surgical



Fig. 2.—The wound eleven days after the operation. There had been no recurrence or spread of the infection. The granulations are active. Zinc peroxide may be seen adherent to the skin and the surface of the wound.

pathologic laboratory for examination was subsequently reported to be "loaded with amebas."

*Treatment.*—In the meantime the patient's general condition improved sufficiently to make us feel that it would be safe to employ surgical intervention. We felt that it was important to remove the whole mass of infected tissue as soon as possible. On the fourth day after admission, therefore, the patient was operated on and a complete excision of the lesion was accomplished. This required removing the skin of the anus, which had become completely undermined. No deep sinus tracts or fistulas were seen along the rectum. The raw surface was dressed with zinc peroxide, and in twenty-four hours the foul odor had entirely disappeared. On the third day after operation the pathologic report of the biopsy was returned and then for the first time the stools were examined for amebas. Actively motile amebas containing red blood cells, typical of *E. histolytica*, were found.

On the basis of these observations the patient was given a course of antiamebic treatment consisting of the daily administration of chiniofon by mouth and emetine hydrochloride by hypodermic injection over a period of two weeks.

The stools were examined on the third day after the treatment had begun and no amebas could be found. Repeated examinations thereafter gave negative results. The diabetes came under control rapidly, and the wound soon showed active granulations. Figure 2 shows the condition of the wound eleven days after operation. On the twenty-first day half the area was covered with skin grafts of the Reverdin type taken from the thigh; the rest of the wound was covered on two successive occasions: four and eleven days after the first graft. Figure 3 shows the wound nine days after the first, and five days after the second, grafting. The whole area rapidly contracted and became epithelialized, and the patient was able to leave the hospital fifty-three days after the primary operation. Ten days later the wound was fully epithelialized except for one or two small areas between grafts in the groin and intergluteal creases (fig. 4).

*Bacteriologic Examination.*—At the time of the operation, cultures were made of bits of subcutaneous tissue just outside the area of gangrene at the lower margin of the lesion on the thigh. Neither aerobic nor anaerobic cultures yielded any growth after prolonged incubation. Cultures of the slough beneath the gan-



Fig. 3.—The wound nine days after the first skin graft and five days after the second graft. The first grafts have already coalesced, and the recent ones are separate.

grenous skin were overgrown with the spreader *Bacillus proteus*. When this mixed culture was heated for fifteen minutes at 60 C., *B. proteus* was killed and green aerobic streptococci survived, but no anaerobic or micro-aerophilic bacteria could be found. *B. proteus* was probably a casual contaminant and probably masked the presence of other bacteria both aerobic and anaerobic which succumbed to the same degree of heat.

*Pathologic Study.*—The tissues were studied by Dr. A. Purdy Stout and Dr. V. Kneeland Frantz of the surgical pathology department and by Mrs. Hulse and Dr. F. W. O'Conner of the department of tropical medicine of the hospital, and all agreed that the amebas were evidently playing a part in the destructive process. A thorough study of the stained sections was made and photomicrographs were prepared by one of us (H. E. M.) (figs. 5 and 6).

The histopathologic process consisted essentially of invasion of the subcutaneous connective tissue and fat by amebas with resulting histologic changes. The most striking feature of the process was a rather sharp line of demarcation

between practically normal tissue and tissue undergoing disintegration. Along this line of demarcation amebas were seen; in some places there were very few, and in others they were crowded together in large groups or in a single line (fig. 5). Some had advanced into the relatively normal tissue and others were scattered in the disintegrated tissue. The relatively normal tissue was somewhat edematous and contained mononuclear wandering cells and polymorphonuclear leukocytes in varying numbers, but never in the large numbers which are ordinarily seen in a pyogenic bacterial infection. The amebas were never very far advanced in this tissue but lay between fat cells or in tissue spaces near the line of demarcation. The disintegration consisted of fragmentation of intercellular fibers and

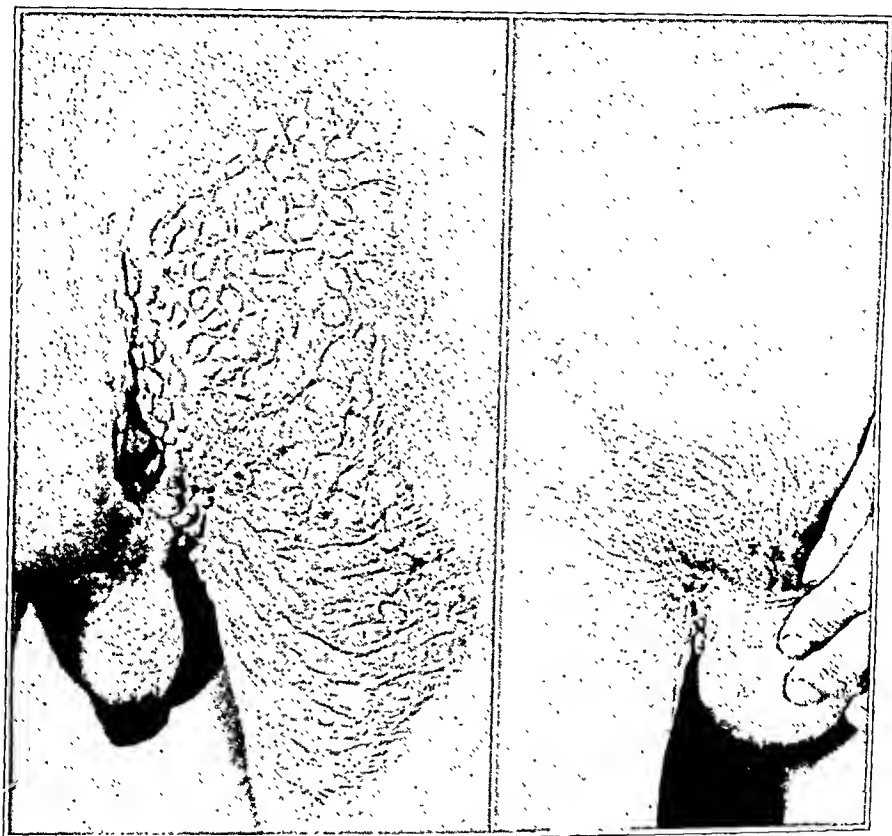


Fig. 4.—The lesion two months after the operation. The wound is completely healed except for one or two spots in the creases of the groin and buttocks. The anal mucous membrane protrudes slightly.

degeneration and nuclear fragmentation of the fixed cells and the mononuclear and polymorphonuclear cells which were present. These cells were more numerous in the disintegrated tissue than in the surrounding relatively normal tissue. Blood and lymph vessels resisted the disintegration more than the rest of the tissue. Occasionally a thrombus was found on the wall of a blood vessel adjacent to the amebic invasion (fig. 6). Amebas were also found in the lumens of some of the small veins and lymph vessels. Farther away from the line of demarcation disintegration was more complete, and blood vessels were destroyed, and at the surface of the ulcer only degenerated cellular elements and amorphous material were seen. Amebas were present in decreasing numbers as the tissue became

more disintegrated until they were practically absent at the surface of the ulcer. In one section a gangrenous condition of the tissue was present to a depth of 1 cm. or more. Amebas were not found in this area, but at the deep margin of the gangrene they were scattered along the edge of the relatively normal tissue. In another section granulation tissue was present at the overhanging edge of the epidermis, with no amebas near it, but amebas were present in the deep advancing portion of the lesion.

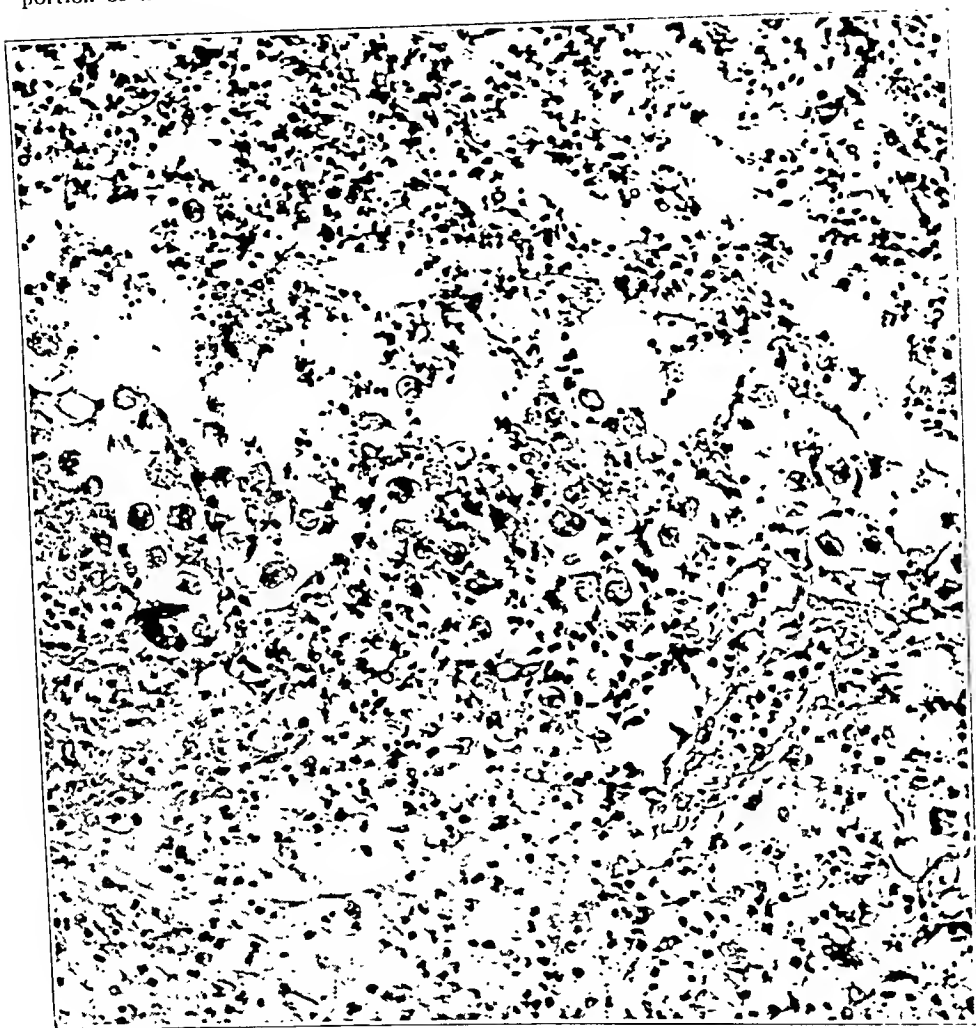


Fig. 5.—Photomicrograph showing amebas at the advancing margin of the ulcer. Note the sharp line of demarcation between the edematous normal tissue infiltrated with wandering cells (below) and the disintegrated tissue (above). Hematoxylin and eosin stain;  $\times 230$ .

Gram stains for bacteria showed gram-positive cocci often in large colonies at the surface of the ulcer and in smaller colonies in the deeper disintegrated tissue, but never as deep as the amebas had advanced and never in the relatively normal tissue beyond the amebas. These cocci were small, were arranged in pairs

and short chains and had the appearance of streptococci. No gram-negative organisms could be seen. If present they must have been very few.

The impression gained from the study of these sections was that the amebas were responsible for the advance of the pathologic process and the disintegration of the tissue. The bacteria seemed to be secondary invaders growing into the already necrotic tissue.



Fig. 6.—Photomicrograph showing a mural thrombus (*T*) in the lumen of a small vein in the subcutaneous tissue near the point of invasion of the amebas (*A*) into the outer layer of the wall of the vessel. Hematoxylin and eosin stain;  $\times 500$ .

#### COMMENT

This case was of interest because of the severity of the infection and the extent of destruction of the skin. Probably the underlying diabetes increased the severity of the symptoms and had something to do with the acuteness of the process. In one of the patients whose

case was reported by M. F. Engman Jr. and one of us (H. E. M.)<sup>16</sup> diabetes was present, and the amebas had invaded even the striated muscle cells of the abdominal wall. In other cases previously reported the onset was more gradual and the course slower.

The condition in this case is sharply differentiated both clinically and bacteriologically from the other forms of chronic infectious gangrene. The differentiation is particularly important between this type and progressive postoperative synergistic gangrene.<sup>18</sup> In that disease the dead skin and subcutaneous slough are adherent all around the margin of the lesion. There is no undermining of the edges of the skin. The outer margin of the gangrene is crenated. The skin outside the gangrene is raised from the surface and is purplish, and this zone is surrounded by a brilliant red zone from 1 to 3 cm. wide which gradually fades off into normal skin. The lesion is excruciatingly tender. In the case reported here there was relatively little gangrene of the skin and the line of demarcation was relatively smooth and sharply outlined. the margin of skin outside the gangrene was not raised, there was no red zone, and the wound was not extremely tender. The margin of the skin elsewhere was extensively undermined and the granulating base of the ulcer was rough and shaggy with necrotic tissue adherent to it.

Although in the present case the clinical appearance of the lesion was quite different from that which we have seen in cases of postoperative synergistic gangrene, other cases of anebic ulceration of the skin may not be so distinctive in their clinical appearance. For example, in the two cases reported by M. F. Engman Jr. and one of us (H. E. M.)<sup>16</sup> an advancing red zone about the ulcers was described, and in one patient the margin of the ulcer was raised and acute tenderness was noted. In some cases of bacterial gangrene amebas may be present as contaminating organisms without taking part in the gangrenous process. In other cases both factors may operate and change the characteristic clinical picture accordingly.

The bacteriologic study confirmed this differentiation, for in the synergistic type of gangrene the essential organism, a micro-aerophilic nonhemolytic streptococcus, may always be found in pure culture of material from the area just outside the margin of the gangrene and is associated with *Staphylococcus aureus* in the gangrene. While *B. proteus* may be a secondary contaminant of any wound from fecal soiling, it may be destroyed by heating to 60 C. for fifteen minutes, while the streptococcus survives. In this case not only were we unable to cultivate this streptococcus from material in the zone outside the gangrene, but

18. Meleney, F. L.: Bacterial Synergism in Disease Processes, with Confirmation of the Synergistic Bacterial Etiology of a Certain Type of Progressive Gangrene of the Abdominal Wall, *Ann. Surg.* 94:961, 1931; footnote 1.

we failed to find it in the gangrenous area itself. The pathologic study likewise confirmed this, for the amebas were found in the advanced zone of infection while the bacteria were in the rear. We cannot be sure, however, that the amebas were not aided by the presence of the bacteria, for we know that cultivation of amebas in vitro without bacteria is at present impossible.

#### SUMMARY

A case of gangrene of the buttocks, perineum and scrotum has been studied from clinical, bacteriologic and pathologic standpoints, and the conclusion has been reached that it was due primarily to the lytic action of *E. histolytica*.

As far as we know, this is the first case that has been studied carefully with anaerobic bacteriologic technic, thus ruling out the presence of the micro-aerophilic nonhemolytic streptococcus which is the essential organism in the progressive postoperative synergistic gangrene with which this disease might be confused. The differential features of these two diseases have been outlined.

The patient made a rapid recovery following the complete excision of the lesion, the administration of a course of chiniofon and emetine hydrochloride, the local application of zinc peroxide and the application of skin grafts.

# LUMBAR VERTEBRAL EPIPHYSITIS

SAMUEL KLEINBERG, M.D.

NEW YORK

For a number of years physicians have recognized the existence in adolescent youths of a disturbance in the epiphyseal rings of the vertebral bodies due to nutritional inadequacy and rapid growth. The condition has been designated, for convenience, vertebral epiphysitis: its clinical appearance and the roentgenographic evidence of pathologic changes are similar to the syndrome occurring in other epiphyses, notably in the head of the femur, the tibial tubercle, the tarsal scaphoid and other similar structures. Vertebral epiphysitis, described by Scheuerman, Buchman and others, has a clinical syndrome which is readily recognized. In brief, the patient, a boy or girl in the early teens, usually without any apparent cause or at times after a seemingly minor trauma, experiences pain in the middorsal area of the back and tires easily. Objectively he presents an abnormal degree of rounding of the back and tenderness to pressure over the dorsal portion of the spine. The roentgenograms show an involvement of from six to eight vertebrae in the middorsal section. There are haziness and reduction in the size of the intervertebral spaces. There is a loss of definition of the outlines of the vertebral bodies. The superior and inferior surfaces are wavy. Frequently there is marked wedging of the vertebrae. This condition continues for some time, but it is self-limited in that toward the end of puberty or within several years of the onset the process terminates, the pain, tenderness and fatigue disappearing more or less completely. But this pathologic condition may, when it gives rise to vertebral wedging, set up a rigid posterior curvature of the spine which may be difficult or even impossible to correct. Buchman expressed the belief that dorsal vertebral epiphysitis may even initiate and be responsible for structural scoliosis.

An interesting and as yet not satisfactorily explained peculiarity of vertebral epiphysitis, of which one sees many instances nowadays, is that it occurs mainly in the dorsal region. My colleague, Dr. Buchman, has seen several cases of epiphysitis of the lumbar vertebrae. The case herein reported is the first one to come under my personal observation and is interesting for several reasons which will be apparent in the clinical detail.



## REPORT OF A CASE

R. B., aged 12 years, came under my care in November 1931. The chief complaints were pain in and stiffness of the lower portion of the back, pain in the thighs, fatigue and inability to engage in vigorous physical exercise. There was no history of trauma. The examination showed that the lad had been growing rapidly and was apparently in good general condition. The posture was poor. The patient presented a moderate degree of dorsolumbar posterior curvature and a slight deviation of the lumbar portion of the spine to the right side. There was



Fig. 1.—Roentgenogram taken in the lateral position, showing the lumbar portion of the spine (November 1931). All the lumbar vertebrae are affected, but the first, second and third show the greatest change. There are rarefaction and some apparent loss of bony substance in the anterior portions of the bodies. The fourth lumbar vertebra has a wavy, somewhat indefinite outline. The intervertebral spaces are not altered.

fairly marked tenderness to pressure over the lumbar portion of the spine and marked limitation of all lumbar movements. Roentgenograms taken in the anteroposterior position showed a mild lumbar scoliosis to the right side. Those taken in the lateral position showed marked changes in all the lumbar vertebrae but the last. These changes consisted of areas of apparent erosion and absorption (fig. 1). The erosion or irregular rarefaction affected the superior anterior por-

tions of the first and second lumbar vertebrae but was especially marked in the third lumbar vertebra. The fourth and fifth vertebrae seemed to have unduly long anteroposterior diameters and appeared somewhat compressed from above downward. The dorsal vertebrae appeared normal.

A diagnosis of advanced lumbar vertebral epiphysitis with secondary scoliosis was made, and a plaster of paris jacket was applied. The boy was allowed to go

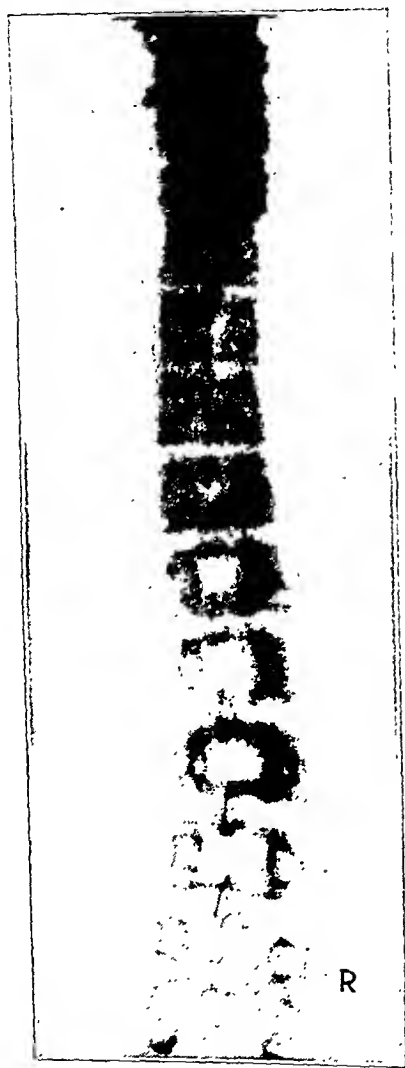


Fig. 2.—Roentgenogram taken in the anteroposterior position (March 1934). There is a mild scoliosis to the right side in the lumbar portion of the spine with a slight compensatory curve to the left in the dorsal portion. Note the wedging of the second and third lumbar vertebrae.

to school, but gymnastic exercises and all strenuous physical activity were interdicted. These instructions were not continuously followed; on many occasions the patient played baseball and ran in races, two types of sport in which he excelled. In January 1932, the plaster jacket applied two months previously was

removed. The condition of the back had improved. The backache and spinal tenderness had disappeared. The posterior curvature seemed corrected. The roentgenograms showed favorable progress; the craters in the vertebral bodies were smaller, and there was definite calcification and ossification of the rarefied areas. A Taylor spinal brace was provided. The patient was reexamined six months later, in June 1932, when he showed signs of continued improvement clin-

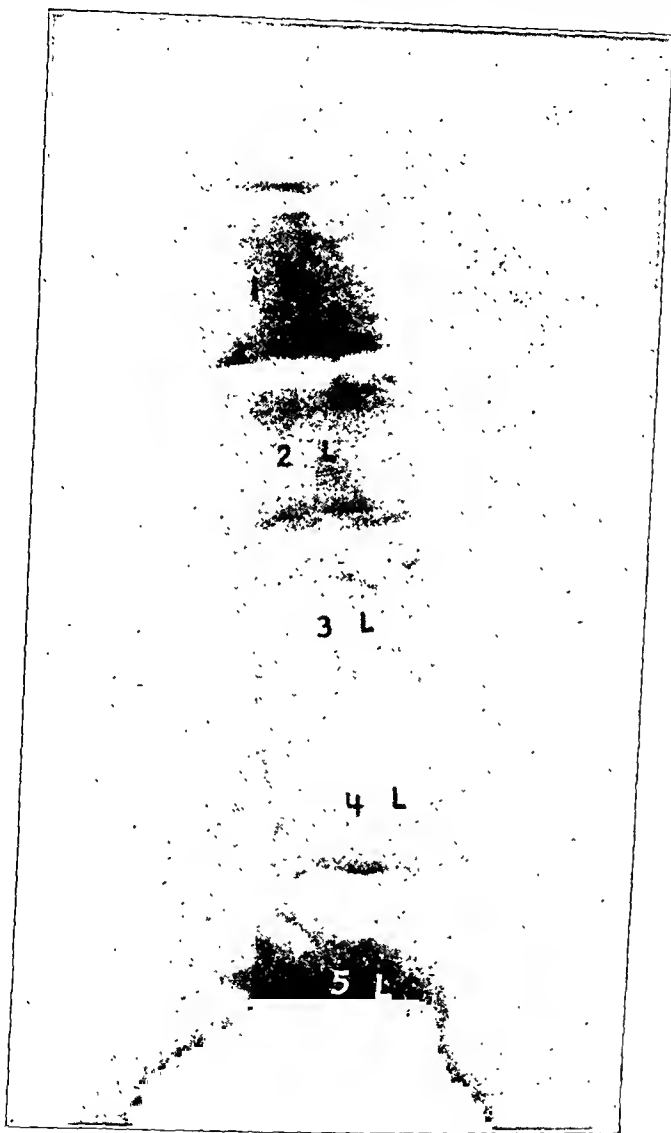


Fig. 3.—Roentgenogram taken in the lateral position (March 1934). The conformation of the vertebral bodies is nearly normal. The area of bone absorption has almost completely disappeared. The crater in the third lumbar vertebra has filled in. The outlines of the vertebrae are more clear. These evidences indicate recession of the pathologic condition and healing.

ically and roentgenographically. Examinations of the blood for the phosphorus, calcium and phosphatase contents gave normal results. He returned thirteen months later, in July 1933, stating that he felt well, had been quite active and had engaged freely in sports without becoming fatigued. The roentgenograms showed seem-

ingly progressive improvement in the conformation and structure of the lumbar vertebrae. But clinically there had been retrogression; the boy's posture was again poor, and there was recurrence of the posterior curvature and tenderness of the lumbar portion of the spine. The possibility of the deformity's increasing was explained to him, and caution was advised. He was provided with a new spinal brace to be worn during the day and with a convex frame on which he was to sleep.

I saw this boy again in March 1934, eight months after the previous visit. During the interval he had grown unusually tall. His mother thought that he had grown about 5 inches (13 cm.). He certainly had completely outgrown the brace. He complained of pain, stiffness and weakness in the back. The examination showed that he had not only a posterior curvature of the spine but a definite lateral curvature to the right side, that is, a lumbar kyphoscoliosis to the right side. Flexion of the spine was almost completely restricted. Hyperextension and lateral inclination were only slightly limited.

In the roentgenogram taken in the anteroposterior position at that time (fig. 2) the second and third lumbar vertebrae appeared wedge-shaped. There was a mild curve to the right side in the lumbar portion, and a compensatory curve to the left in the dorsal portion of the spine. A roentgenogram taken in the lateral position (fig. 3) showed an improvement in the epiphyseal changes. There was almost complete restoration of the normal conformation of the vertebrae, with decided diminution of the rarefaction and increased ossification. The first lumbar vertebra showed only a slight defect in the upper anterior corner. There was decided increase in the density of the bone in the upper and lower surfaces of the second lumbar vertebra; the crater-like formation in the third lumbar vertebra had disappeared and was replaced by a moderate amount of rarefaction in the upper surface of the body of that vertebra. The outline of the third lumbar vertebral body was practically normal. The fourth lumbar vertebra showed some waviness and rarefaction of its upper surface. The intervertebral spaces were clear and free from any bony projections. This roentgenogram when compared with the first one made two and a half years before showed a marked change for the better in the structure of the lumbar vertebrae, although clinically the boy was far from well. A plaster of paris jacket was immediately applied to correct the kyphoscoliosis and provide rest for the back. I had learned by then that this boy's activity could be controlled or restricted only by a mechanical hindrance such as a plaster jacket. His promise to rest could not be relied on. In July 1934 the patient had no pain and no spinal tenderness. He still had stiffness of the back. He was wearing a spinal brace and taking regulated gymnastic exercises to improve the muscle tone and to increase the mobility of the spine.

#### DIFFERENTIAL DIAGNOSIS

In arriving at a diagnosis of this patient's lesion there were, from a practical standpoint, only two conditions to consider, namely, Pott's disease and osteochondritis. If the condition had been tuberculosis of the spine the history would have indicated and the examination would have revealed greater disability. Moreover, the roentgenograms would have shown irregular destruction and absorption of bone, disappearance of the intervertebral cartilage, formation of an angular deformity or gibbus and possibly one or more cold abscesses and evidences of pressure on the spinal cord. In tuberculosis when several vertebrae are involved in an extensive destructive process the central vertebra dis-

appears partially or totally and the adjacent vertebrae above and below it become approximated. The absence of all these findings permitted an unqualified exclusion of the diagnosis of tuberculosis of the lumbar portion of the spine.

In osteochondritis of a vertebrae, as the literature indicates, there is usually involvement of only one vertebra which is widened in its transverse and reduced in its vertical diameter. The superior and inferior epiphyseal plates are practically unchanged. In epiphysitis and in the case here reported the essential pathologic change is in the epiphyseal plates and not in the substance of the body. Consequently it was reasonable to eliminate the diagnosis of osteochondritis.

#### COMMENT

In retrospect it appears that a more favorable result would have been obtained if, when the diagnosis of vertebral epiphysitis was established, I had insisted on rigid and continuous support of the spine by a brace during the day, avoidance of all strenuous physical activity and competitive games and the use of a convex frame at night. By such measures the process of epiphyseal dysfunction may have been aborted, ossification hastened and the scoliosis possibly prevented. The more cases of epiphyseal growth disturbances I study and the more patients I treat, the more I am convinced that rest to the affected part is the most effective therapeutic agent. In parts of the body other than the spine, I have been able to combat epiphysitis by enforced rest and have succeeded in obtaining rapid and complete cures. In epiphyseal disturbances of the spine occurring during the period of growth, abstinence from weight bearing, as nearly complete as possible, is the essential requirement in the therapeutic program.

#### SUMMARY

A case of lumbar vertebral epiphysitis in an adolescent boy is reported.

The changes observed roentgenographically are similar to those seen in dorsal vertebral epiphysitis and are fairly characteristic of this condition.

The patient has been observed for nearly three years. During this time the pathologic changes in the bones have retrogressed, but a mild lumbar kyphoscoliosis has appeared.

The subjective symptoms of pain in and weakness of the back and fatigue were easily controlled by mechanical supports.

The changes in the vertebral epiphyses are undoubtedly due to nutritional inadequacy arising from inordinately rapid growth.

This case is of special interest because vertebral epiphysitis rarely affects the lumbar vertebrae.

# SURGICAL TREATMENT OF EPENDYMAL GLIOMA OF THE SPINAL CORD

LEO J. ADELSTEIN, M.D.  
AND  
GEORGE H. PATTERSON, M.D.  
LOS ANGELES

Tumors of the central nervous system having their origin from ependymal cells have long been looked on as a rarity. The reports of workers in the various clinics, particularly of those interested in tumors of the brain, reveal but a relatively small number of ependymal gliomas found in the encephalon. In 1926 Bailey and Cushing<sup>1</sup> reported 7 ependymomas among 254 classified gliomas. In a later study Bailey<sup>2</sup> found 16 ependymal tumors during an analysis of 566 gliomas. Fincher and Coon<sup>3</sup> in 1929 reviewed 8 cases found among 140 cases of glioma at the Sachs clinic. The ependymomas, therefore, would seem to comprise but a small percentage of the glioma family as found in the brain.

The careful investigations of Kernohan, Woltman and Adson<sup>4</sup> have revealed a different situation with regard to the number of ependymal tumors found as intramedullary tumors of the spinal cord. In an analysis of 51 verified intramedullary tumors of the spinal cord these authors found 21 ependymomas, or an incidence of 42 per cent. which would seem to place this group among the common parenchymatous tumors of the spinal cord.

## LITERATURE

Two communications by Bailey<sup>5</sup> which appeared in 1924 and 1925 furnish a complete summary of the pathologic picture presented by

---

Read before the section on Neuropsychiatry at the Sixty-Third Annual Session of the California Medical Association, May 2, 1934.

From the Neurosurgical Service of Dr. Carl W. Rand and Dr. George H. Patterson, Los Angeles County General Hospital, and the Department of Neurological Surgery, University of Southern California, School of Medicine.

1. Bailey, Percival, and Cushing, Harvey: A Classification of the Tumors of the Glioma Group, Philadelphia, J. B. Lippincott Company, 1926, p. 175.

2. Bailey, P.: Further Remarks Concerning Tumors of the Glioma Group, *Bull. Johns Hopkins Hosp.* 40:354 (June) 1927.

3. Fincher, E. F., and Coon, G. P.: Ependymomas: A Clinical and Pathologic Study of Eight Cases, *Arch. Neurol. & Psychiat.* 22:19 (July) 1929.

4. Kernohan, J. W.; Woltman, H. W., and Adson, A. W.: Intramedullary Tumors of the Spinal Cord, *Arch. Neurol. & Psychiat.* 25:679 (April) 1931.

5. Bailey, P.: A Study of Tumors Arising from Ependymal Cells, *Arch. Neurol. & Psychiat.* 11:1 (Jan.) 1924; Quelques nouvelles observations des tumeurs ependymaires, *Ann. d'anat. path.* 2:481 (Nov.) 1925.

gliomas of ependymal origin. On further review one finds numerous references with excellent descriptions of these tumors. The classic description by Saxer<sup>6</sup> appeared in 1902 and was followed shortly by Mallory's<sup>7</sup> important paper describing 3 ependymal gliomas. The importance of the latter contribution lies in the fact that Mallory actually demonstrated the origin from ependymal cells of the tumors in his 3 cases. Spiller<sup>8</sup> reported 2 extremely interesting cases in 1903 and 1907, in 1 of which he regarded the growth as a spinal metastasis from a typical growth in the fourth ventricle. Penfield's<sup>9</sup> résumé of the ependymal tumors is clear and concise and furnishes common ground for the descriptions given by Roussy, Lhermitte and Cornil,<sup>10</sup> and Roussy and Oberling<sup>11</sup> in their monographs on a group of gliomas under the term ependymoglioma. Orlandi<sup>12</sup> in 1925 and Silberberg<sup>13</sup> in 1926 described single cases, and at about the same time appeared the paper of Hirsch and Elliot<sup>14</sup> with a report of 2 additional cases, in each of which the tumor arose in the lateral and fourth ventricles.

The ependymomas are situated most frequently in the posterior fossa near the midcerebellar region, probably arising from the roof of the fourth ventricle and many times growing down through the foramen magnum. In one of Spiller's<sup>8a</sup> cases the tumor grew down from the fourth ventricle to the level of the sixth cervical vertebra. In 5 of the Fincher-Coon<sup>3</sup> series of 8 cases the tumor was located in the cerebrum close to the lateral ventricles and, as the authors indicated, there was no predilection for any particular portion of the lining of the lateral ventricles as a site of origin.

---

6. Saxer, F.: Ependymepithel, Glioma und epithiale Geschwülste des Centralnervensystems, *Beitr. z. path. Anat. u. z. allg. Path.* **32**:276, 1902.

7. Mallory, F. B.: Three Gliomata of Ependymal Origin: Two in the Fourth Ventricle, One Subcutaneous Over the Coccyx, *J. M. Research* **8**:1 (June) 1902.

8. (a) Spiller, W. G., and Hendrickson, W. F.: A Report of Two Cases of Multiple Sarcomatosis of the Central Nervous System and One Case of Intramedullary Primary Sarcoma of the Spinal Cord, *Am. J. M. Sc.* **126**:10 (July) 1903. (b) Spiller, W. G.: Gliomatosis of the Pia and Metastasis of Glioma, *J. Nerv. & Ment. Dis.* **34**:298 (May) 1907.

9. Penfield, Wilder: Principles of the Pathology of Neurosurgery, in Nelson Loose-Leaf Living Surgery, New York, Thomas Nelson & Sons, 1927, vol. 2, chap. 6, p. 303.

10. Roussy, G.: Lhermitte, J., and Cornil, L.: Essai de classification des tumeurs cérébrales, *Ann. d'anat. path. méd.-chir.* **1**:333, 1924.

11. Roussy, G., and Oberling, C.: Atlas du cancer, Paris, Felix Alcan, 1931.

12. Orlandi, H., quoted by Bailey,<sup>2</sup> p. 375.

13. Silberberg, E.: Neuroblastoma und Neuroepithelioma, *Virchows Arch. f. path. Anat.* **260**:251, 1926.

14. Hirsch, E. F., and Elliot, A. R.: Ependymomas of the Lateral and Fourth Ventricles of the Brain, *Am. J. Path.* **1**:627, 1925.

The frequency with which these tumors arise primarily in the spinal cord has never been stressed, nor has their surgical accessibility been generally recognized. Bickel,<sup>15</sup> Jumentie,<sup>16</sup> Holmes and Kennedy<sup>17</sup> and Dejerine and Jumentie<sup>18</sup> have reported cases of ependymal tumor arising in the spinal cord. Cases of tumor with a similar origin described under the term neuro-epithelioma have been cited by Rosenthal,<sup>19</sup> Kling,<sup>20</sup> Schlapp<sup>21</sup> and others, which would indicate that the spinal cord is not an uncommon locus of origin. Perhaps the most interesting individual report of a case is the one by Cushing,<sup>22</sup> whose graphic description bears quotation since it clearly visualizes the technical problems involved in the removal of such a tumor.

The patient, an 8 year old girl, was referred to the clinic of the Peter Bent Brigham Hospital on Sept. 8, 1926, with a diagnosis of possible syringomyelia. The history was essentially as follows:

"In October 1924, she complained of a stiff neck and had a temporary 'torticollis.' After eight weeks of treatment by a local physician at her home she gradually recovered, and remained well until September 1925, when she had a recurrence of the 'torticollis' with pain in the neck. She nevertheless was able to attend school at irregular intervals during the ensuing school year. In July 1926, after several chiropractic treatments there was an increase in symptoms with a distinct change in the condition—more severe pain and muscular weakness of the arms. Doubtless under the suspicion that she had cervical Pott's disease, a local surgeon had her wear a Thomas collar.

"The most striking thing, objectively, on admission was the curious fixed and rigid position in which she held her head. Any attempt to change this position caused pain. There was an exaggeration of the deep reflexes, muscular weakness of both upper extremities with considerable atrophy, particularly marked in the intrinsic muscles of the hands. There was thought to be some dissociation of sensation, but the sensory symptoms were exceedingly slight and variable. The differential diagnosis lay between cervical Pott's disease (though there were no

---

15. Bickel, M. G.: Contribution à l'étude des tumeurs de la moelle épinière et de la syringomyélie, *Ann. de méd.* **10**:253 (Oct.) 1921.

16. Jumentie, J.: Tumeur de la moelle lombo-sacrée et formations glieuses du type syringomyélique, *Rev. neurol.* **34**:741 (Dec.) 1927.

17. Holmes and Kennedy: Syringomyelia Without Symptoms Associated with Intracranial and Spinal Tumors, *Proc. Roy. Soc. Med.* **2**:4, 1908.

18. Dejerine, J., and Jumentie, M. J.: Tumeur intramedullaire de nature complexe, *Rev. neurol.* **37**:1138 (Nov. 3) 1921.

19. Rosenthal, W.: Ueber eine eigentümliche mit Syringomyelie complizierte Geschwulst des Rückenmarks, *Beitr. z. path. Anat. u. z. allg. Path.* **23**:111, 1898.

20. Kling, C. A.: Ein Beitrag zur Kenntnis der Rückenmarkstumoren und Höhlenbildungen im Rückenmark, *Ztschr. f. klin. Med.* **63**:322, 1907.

21. Schlapp, M. G.: Neuro-Epithelioma Developing from a Central Gliosis, After an Operation on the Spinal Cord, *J. Nerv. & Ment. Dis.* **38**:129 (March) 1911.

22. Cushing, H.: The Intracranial Tumors of Preadolescence, *Am. J. Dis. Child.* **33**:551 (April) 1927.



bony lesions shown by the roentgen ray), syringomyelia and tumor of the cord. Each of these diagnoses had its firm supporters. . . .

" . . . I went ahead with a cervical laminectomy, which, before the end, was extended so as to include all of the cervical and the two upper thoracic vertebrae.

"An extraordinary condition was found. The canal . . . was greatly distended, so that the flattened laminae were removed easily, giving an unusually wide exposure. When the dura was opened and reflected, no fluid was secured, and a bulging cord presented. One could see through the thinned nervous tissue that there was a central tumor. A longitudinal incision, the length of the entire wound, through the greatly thinned posterior columns, disclosed a central soft reddish tumor mass which began spontaneously to extrude itself. With a 'sucker,' it was cleanly removed, leaving a widely dilated, thinned out gutter of nervous tissue.

"I can only liken the procedure to the splitting of an over-ripe banana with the removal by suction of its central fruit, leaving the collapsed skin behind. The upper pole of the tumor was at the level of the foramen magnum, and not until this portion of the growth was removed did cerebrospinal fluid begin to find its way down into the gutter. The lower pole of the tumor extended below the second thoracic level, and it was thought wise to postpone further measures for a second session.

"The tumor, which presumably extends much further down the cord, proves to be an ependymoma and has therefore arisen from the central canal. Now that she has made such an excellent recovery we propose to laminectomize the remainder of the spine and to clean out what remains of the lesion in the lower levels, for it fortunately is a relatively benign type of glioma and is not infiltrative in character.

"*Subsequent Note.*—The second laminectomy exposing the remainder of the cord from the second thoracic to the second lumbar vertebrae inclusive was carried out on November 2. When the cord was exposed I found to my surprise that the tumor ended at about the second thoracic level with nothing below but a marked hydromyelia. The patient was discharged on November 27, walking, with free cervical movements, return of function in her hands, and little to show for her former trouble except overactive reflexes."

A rather unusual type of surgical removal for this kind of tumor was used in this case, since the majority of these neoplasms are quite firm and encapsulated and may be separated from the spinal cord only by gentle blunt dissection. The association with hydromyelic or syringomyelic cavities is almost a constant finding in cases of tumor of this type, and according to Dowman and Smith<sup>23</sup> such cysts suggest the presence of an intramedullary tumor.

#### PATHOLOGY

The ependymal gliomas have passed through many phases in the gradual evolution of a rather confusing nomenclature. Formerly the

---

23. Dowman, C. E., and Smith, W. A.: Intramedullary Cyst of the Spinal Cord Associated with a Circumscribed Intramedullary Tumor, *Arch. Neurol. & Psychiat.* **21**:582 (March) 1929.

terms neuro-epithelioma, ependymoblastoma and ependymoglioma were given to one and the same type of tumor. The subdivisions of the family group into ependymoblastoma and ependymoma have been recognized as being mainly transitional forms, and the characteristics of the two groups differ little. At present an ependymoma is considered in simple terms to be that type of glioma which enters into the formation of ependymal epithelium, and its general family name has been simplified by the use of the term ependymal glioma or ependymoma. This tumor seems by structure to be derived from the ependymal lining of the cerebral ventricles and spinal canal. The tumor is usually rather firm, encapsulated and sometimes nodular and shows tendencies to undergo calcification and the formation of cysts. In the spinal cord the

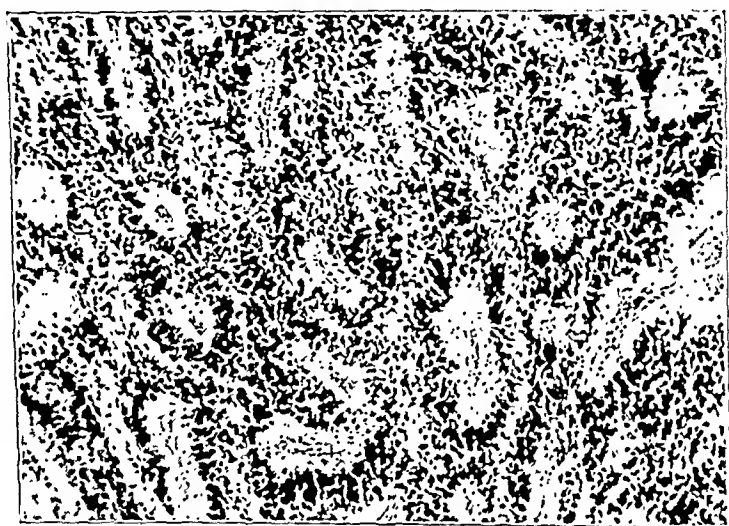


Fig. 1.—A section of an ependymal glioma (ependymoblastoma), showing the formation of pseudorosettes about small blood vessels. Hematoxylin and eosin stain;  $\times 95$ .

origin, as indicated, is from the ependymal lining of the central canal, the tumor being very slow growing and gradually producing the signs and symptoms of an intramedullary neoplasm.

Microscopically these tumors are very cellular. They are characterized by an array of cells about blood vessels to form pseudorosettes. Between the nuclei of the cells and the walls of the central blood vessel is a clear zone occupied by the tail-like processes. There is but little free fat, but the connective tissue about numerous well formed blood vessels gives the appearance of a stroma. Calcification is occasionally found in the central portions of the tumor. Mitotic figures are usually not seen. Mallory<sup>7</sup> stressed as a peculiar and characteristic feature of ependymal cells the cytoplasmic granules or rods previously described by Weigert. He discovered such structures in the neoplastic cells and

concluded that in new growths of ependymal origin such granules or markings (blepharoplasts) would be found. These cytoplasmic markings are, therefore, a useful diagnostic finding, as blepharoplasts are to be found only in ependymal cells and, according to Horrax and Bailey,<sup>24</sup> in pineal cells. The specific methods of staining with metals, such as the Hortega silver carbonate (lithium) stain,<sup>3</sup> serve to bring out the fine detail necessary to establish the relationship of the various neoplastic elements to embryonic forms as found in the histogenesis of normal nerve tissue. The cytoplasm is particularly well demonstrated with Bailey's ethyl violet-orange G and with Mallory's phosphotungstic acid and hematoxylin stain. However, these tumors may be identified as routine with the hematoxylin and eosin stain<sup>25</sup> which reveals clearly the characteristic tissue architecture and nuclear detail (fig. 1).

#### SURGICAL ASPECTS

The pioneer work of Kernohan and his associates<sup>4</sup> has added encouragement to study of the problem of the intramedullary gliomas of the spinal cord of ependymal origin. The realization that this type of glioma is relatively common, has benign tendencies, and in many cases is surgically accessible has led to a careful reconsideration of what has long been looked on as a practically hopeless situation. Foerster,<sup>26</sup> Elsberg,<sup>27</sup> Frazier<sup>28</sup> and many others have reported good results from the removal of tumors of the spinal cord of intramedullary origin. The more recent efforts have been along conservative lines and with good reason. The spinal cord withstands manipulation poorly, and rough handling during the surgical procedure involved in the removal of a neoplasm, not only may leave the patient completely paralyzed afterward but in the upper thoracic and cervical levels may cause early death by respiratory failure or by fatal hyperthermia. In 1911 Elsberg and Beer<sup>29</sup> originated the so-called "extrusion method" for the removal of intramedullary tumors. This method entails a two stage operation. At the first session the tumor is located by incising the posterior columns, and at the second operation as much of the tumor as has extruded

24. Horrax, G., and Bailey, P.: Pineal Pathology, Arch. Neurol. & Psychiat. **19**:394 (March) 1928.

25. Courville, C. B., and Adelstein, L. J.: Tumors of the Glioma Group—Their Histologic Diagnosis, California & West. Med. **34**:396 (June) 1931.

26. Foerster, C.: Zur Diagnostik und Therapie der Rückenmarkstumoren, Deutsche Ztschr. f. Nervenhe. **70**:64, 1921.

27. Elsberg, C. A.: Tumors of the Spinal Cord, New York, Paul B. Hoeber, Inc., 1925.

28. Frazier, C. H.: Surgery of the Spine and Spinal Cord, New York, D. Appleton & Company, 1918, p. 584.

29. Elsberg, C. A., and Beer, E.: The Operability of Intramedullary Tumors of the Spinal Cord, Am. J. M. Sc. **142**:636, 1911.

itself is removed. By this method minimum injury to the cord itself is produced. This technic has found favor in many hands and is the method of choice for the removal of tumors which are soft, infiltrating and with little or no line of demarcation. Others, like Jonesco-Sisesti<sup>30</sup> who reviewed 19 cases of intramedullary tumor associated with syringomyelic cavities, believe that surgical measures for intramedullary tumors should be limited to decompressive laminectomy followed by roentgen therapy. In 1931 Cairns and Riddoch<sup>31</sup> reported the successful removal of ependymal glioma of the spinal cord in 2 patients, in 1 of whom the tumor was located in the cervicothoracic region and in the other, in the thoracic portion, of the spinal cord. Both tumors were completely removed with good results. Their technic is one closely following that of Elsberg which appeared some years ago and which we feel will bear revival at this time.

During the past two years, 2 patients with ependymal tumor of the spinal cord have been seen in this clinic. Both have come to operation, and it is felt that a report of their cases in full is warranted because the cases emphasize the pitfalls in diagnosis as well as the many details and scrupulous care necessary in the successful handling of patients with intramedullary tumors. In agreement with Cairns and Riddoch it must be recognized that the need for meticulous and painstaking after-care is of paramount importance in cases of this type.

#### REPORT OF CASES

*CASE 1.—Intramedullary ependymoma of cervicothoracic portion of spinal cord. Complete removal in one stage operation. Marked improvement.*

*History.*—M. I., a white man 25 years old, a millinery operator, referred by Dr. David Rosenblum, Los Angeles, was first seen in January 1932, with a complaint of numbness and tingling in the right leg followed by progressive weakness of the limb. These symptoms were first noticed in November 1931. Three weeks after the onset the patient noticed that he dragged the right leg in walking and that the right hand and arm were also becoming weak. This was followed within a short time by a similar progression of symptoms in the left arm and hand. Examination in January 1932 revealed horizontal nystagmus, marked intention tremor and absence of abdominal reflexes, on the basis of which the tentative diagnosis of multiple sclerosis was based. The patient then returned to his work as a millinery operator until May, by which time there had developed marked weakness with atrophy of the small muscles of both hands. However, he could still walk about, though with difficulty, and at no time was there any bladder disturbance. Constipation had been marked for some six months prior to his admission to the Los Angeles County General Hospital on June 29.

30. Jonesco-Sisesti, N.: *Tumeurs medullaires associées à un processus syringomyélique*, Paris, Masson & Cie, 1929.

31. Cairns, H., and Riddoch, G.: *Observations on the Treatment of Ependymal Gliomas of the Spinal Cord*, Brain 54:117, 1931.

*Examination.*—The pupils were small, regular and approximately equal and reacted fairly well to light and in accommodation. There were many nystagmoid jerks on looking to the right. These were not considered to be definite nystagmus. The optic disks were well outlined. The nerve heads appeared rather paler than normal. The remainder of the cranial nerves were carefully examined and found to be within normal limits.

There were marked weakness and atrophy with almost complete loss of grip in both hands; the right arm and hand were much more involved than the left. The lower extremities were very weak—the right leg could scarcely be raised off

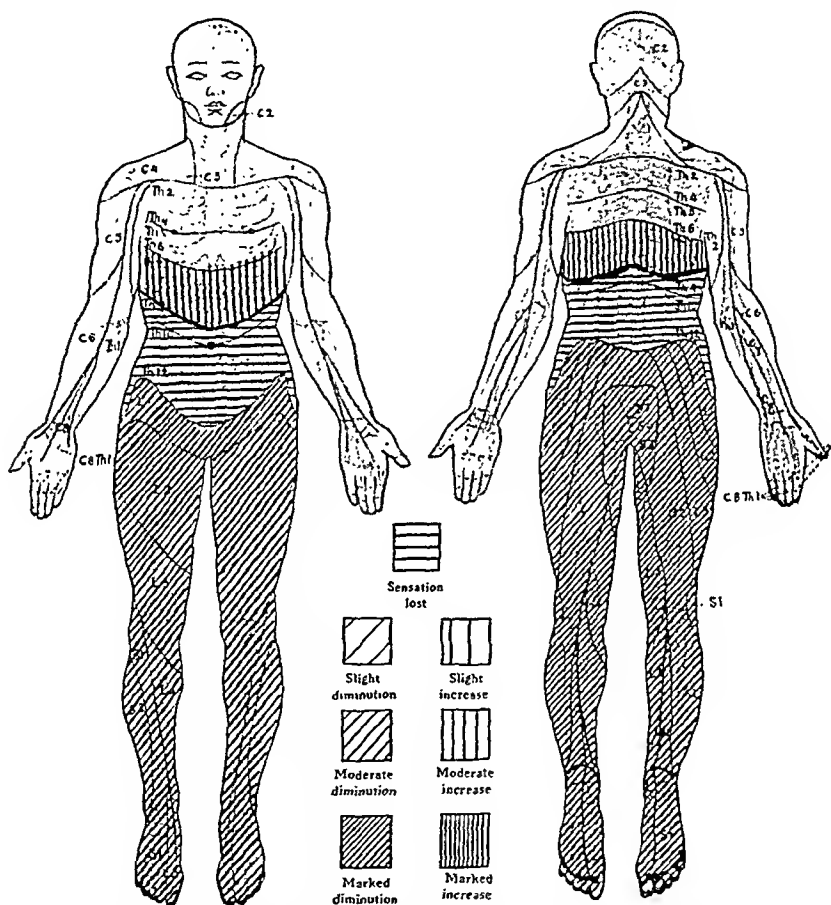


Fig. 2 (case 1).—A diagram showing the cutaneous sensory disturbances in a patient with an intramedullary tumor at the sixth cervical segment.

the bed; the left leg was a little stronger but also presented marked muscular weakness. The deep reflexes were generally increased with the exception of those in the upper extremities. The biceps and triceps reflexes were very weak, particularly on the right. The abdominal and cremasteric reflexes were absent. The knee jerks were markedly increased and there were bilateral ankle clonus and Babinski, Gordon and Oppenheim signs.

There was a sensory level at the sixth cervical segment below which perception of light touch was practically absent (fig. 2). Position sense was completely lost in the right toes, foot, ankle and knee and was only fair in the left lower extremity.

In both the upper and the lower limbs sensation of hot and cold was difficult to differentiate. Vibration sense was completely absent as high as the fifth dorsal segment. On only one occasion did the patient complain of severe pain shooting down both arms. This occurred on his trying to get into bed after taking a short walk. It was thought that the sensory picture was generally that of an atypical Brown-Séquard syndrome with greater sensory symptoms on the right side than on the left.

Roentgen examination of the cervical portion of the spine revealed no characteristic pathologic change, particularly no evidence of bony involvement. The cervical portion of the spine was not tender on palpation. Examination of the spinal fluid revealed a small amount of slightly xanthochromic fluid with an initial pressure of 190 mm. There was no rise in pressure following bilateral jugular compression. There were 24 lymphocytes per cubic millimeter, and the globulin content was markedly increased.

*Diagnosis.*—At this time there was conclusive evidence of a probable neoplasm of the spinal cord, having its upper limit at approximately the sixth cervical segment. The almost complete absence of irritation of the roots and the difficulty in recognizing hot and cold suggested a neoplasm of intramedullary origin. The preoperative suggestion, however, was endothelioma on the right side of the cord.

*Operation.*—An incision was made from the sixth cervical to the first dorsal vertebra and wide laminectomy was performed. The dura was opened with a longitudinal incision, and a dry pulseless tumor was found at the level of the seventh cervical vertebra. The mass was reddish, soft and friable and apparently had an intramedullary point of origin. It became apparent at this point that a larger approach would be necessary, so the fifth cervical spinous process was removed and its corresponding laminae. With careful blunt dissection the superior surface of the tumor was gently dislocated from its surrounding bed of cord substance (fig. 3). Multiple sutures placed through the tumor provided the necessary traction to hold the neoplasm gently and enabled the surgeon to tilt the superior pole of the mass away from the cord. By gently continuing blunt dissection the entire mass, perhaps 5.5 cm. in length, was removed. The vascular pedicle was secured with silver clips and divided. The appearance of the spinal cord after removal of the tumor was that of a thin cuff of nerve tissue with a deep central gutter. The dura was left unclosed in order to provide sufficient decompression for any postoperative edema of the cord. The wound was then carefully closed in layers with no. 2 chromic catgut for the muscles and fascia and black silk for the subcutaneous and cutaneous layers. The condition of the patient at the end of the operation was fair. Ether anesthesia was used throughout the session.

*Postoperative Course.*—The immediate effects of surgical intervention were disconcerting, as quadriplegia with involvement of both sphincters appeared to have been produced and it was feared that the surgical trauma had probably completed the picture begun by the tumor. However, the patient began a slow but definite improvement. The postoperative course was further complicated by severe cystitis, but this gradually subsided. The wound healed well, and the patient was discharged to his home on September 13.

For the first day after the operation the pulse rate remained at an average of 120, returning gradually to 90 within five days. The temperature rose to 101.5 F., at which point it fluctuated for about ten days. Motor and sensory power were completely absent for almost two weeks. On the sixteenth day the legs and fingers could be moved slightly, and on the same day the patient voided spontaneously. From this date improvement was progressive. Changes in sensation

took place very slowly. Physical therapy was instituted early and the patient was closely observed in the neurologic outpatient department. By November 15 the patient had gained 25 pounds (11.3 Kg.) and had full control of both sphincters. The grips were good, and he was attempting to walk with fair results. On Jan. 10, 1933, the patient was walking with the aid of crutches. On April 4 he was walking with the aid of a cane. No definite sensory level could be determined. Muscular strength was good, and the grips were excellent. The reflexes generally were hyperactive, being greater on the right, with no pathologic reflexes. In June 1933,



Fig. 3 (case 1).—A drawing showing the condition found at operation, during which the tumor was removed at one session.

scarcely a year after the operation, the patient was walking about without aid and apparently was in excellent condition. In September he was considering the possibility of returning to his work as a millinery operator in a local factory. It is felt that the ultimate result in this case will be satisfactory and that the patient may become a self-supporting and able citizen.

*Pathologic Examination.*—The tumor (fig. 4) measured 5.8 by 2.1 by 1.8 cm. in its greatest diameters. It appeared to be encapsulated, with a smooth outer surface, and tapered somewhat at its lower pole. It was rather firm in structure, although with a rather fluctuant feel in the upper portions. The cut section revealed soft yellowish-white tissue which in some areas appeared to be degenerated and

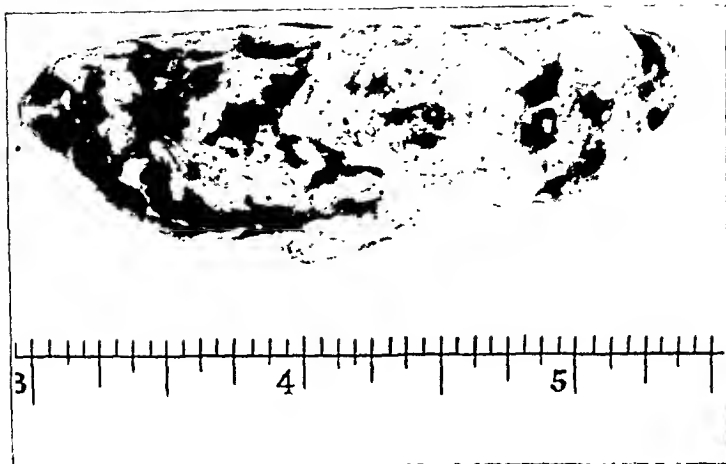


Fig. 4 (case 1).—An ependymal glioma after removal from the cervicothoracic portion of the spinal cord.

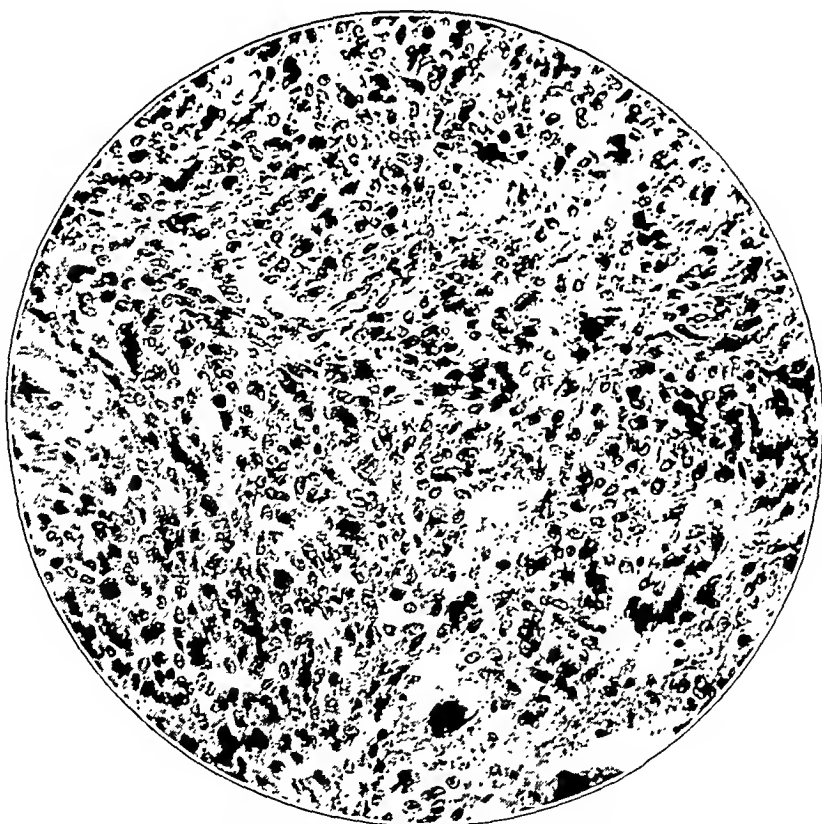


Fig. 5 (case 1).—A section of an ependymal glioma (ependymoblastoma) showing the markedly cellular character. Hematoxylin and eosin stain;  $\times 220$ .



hemorrhagic. The fluctuant feel of the tumor was due to a degenerated central portion of the mass. This hemorrhagic degenerated portion extended throughout the entire tumor, and the lower pole revealed clots indicating recent hemorrhage. The histologic (fig. 5) examination revealed a rather cellular tumor with the cells tending to be grouped about clear spaces and blood vessels. In the midportion of the tumor was a definite epithelial lining of what was probably a central cyst. The diagnosis was ependymal glioma, probably of ependymoblastic type.

*Comment.*—This case is an example of one of the many diagnostic errors that may be made in attempting to identify the clinical picture of an intramedullary tumor of the spinal cord. For about six months this patient was thought possibly to have multiple sclerosis before it was recognized that a localized lesion of the cord was present. However, the result to date has been quite satisfactory, and at least our diagnostic wits have been sharpened by this experience.

*CASE 2.*—*Intramedullary ependymoma of the thoracic portion of the spinal cord. Complete removal of tumor at a second operation. Death due to meningitis.*

*History.*—B. E., a nurse 24 years old, was first admitted to the outpatient department of the Los Angeles County General Hospital on Feb. 1, 1932, with a complaint of pain in the back and weakness of both lower extremities. In 1927 she fell from a horse and since then had suffered severe backache in the lumbar region. Pain, which had been constant during the preceding three years, was aggravated by motion and was frequently associated with a sense of constriction about the waist. Until March 1930 the patient had been able to swim, dance and otherwise use all the extremities freely. About this time she noticed that her right ankle began to weaken and twisted easily; the right leg also gradually became weak and at times felt numb. During the nine months previous to admission to the hospital the left leg became similarly involved, and at the time of her first admission to the hospital both legs felt very numb and the patient was unable to locate the position of her feet without looking at them. Backache at this time was quite severe. The history otherwise was essentially irrelevant.

*Examination.*—Examination revealed a bright woman complaining of severe lumbar pain. The pupils, optic disks and cranial nerves were normal. There was weakness of both lower extremities with the legs about equally affected. On walking there was a slow, shuffling gait which did not seem to be particularly spastic. The biceps, triceps and radial reflexes were present and equal. The knee jerks were practically absent, and the achilles tendon jerks were present but very sluggish. There were no Babinski, Gordon and Oppenheim reflexes or ankle clonus.

There was a sensory level (fig. 6) at the ninth dorsal segment, below which all forms of sensation were markedly disturbed. Touch, pain and vibratory sensation were greatly diminished, and there was marked analgesia to pinprick. Sensation in the upper extremities was normal. Palpation over the spinous processes from the ninth to the twelfth dorsal vertebra produced pain and discomfort. There were no trophic disturbances.

Roentgen examination of the entire dorsolumbar portion of the spine revealed no material pathologic change.

Lumbar puncture revealed yellow cerebrospinal fluid under 100 mm. of pressure. There was no rise of pressure on jugular compression, revealing a complete subarachnoid block. Puncture of the cisterna magna revealed clear fluid under 80 mm. of pressure. The fluid withdrawn from the lumbar canal contained an increased amount of globulin and 10 lymphocytes. The urinalysis and blood picture were normal.

*Diagnosis.*—That the patient was suffering from a tumor of the spinal cord at about the level of the ninth dorsal segment was readily recognized, and with the marked amount of disturbance in the pain and temperature senses an intramedullary location was favored.

*Operation.*—On March 10, with the patient under ether anesthesia, a laminectomy was performed, removing the laminae of the seventh to the eleventh dorsal vertebra, inclusively. The dura appeared to be unusually tense, and on opening it the spinal cord immediately began to herniate; at the level of the eighth dorsal vertebra

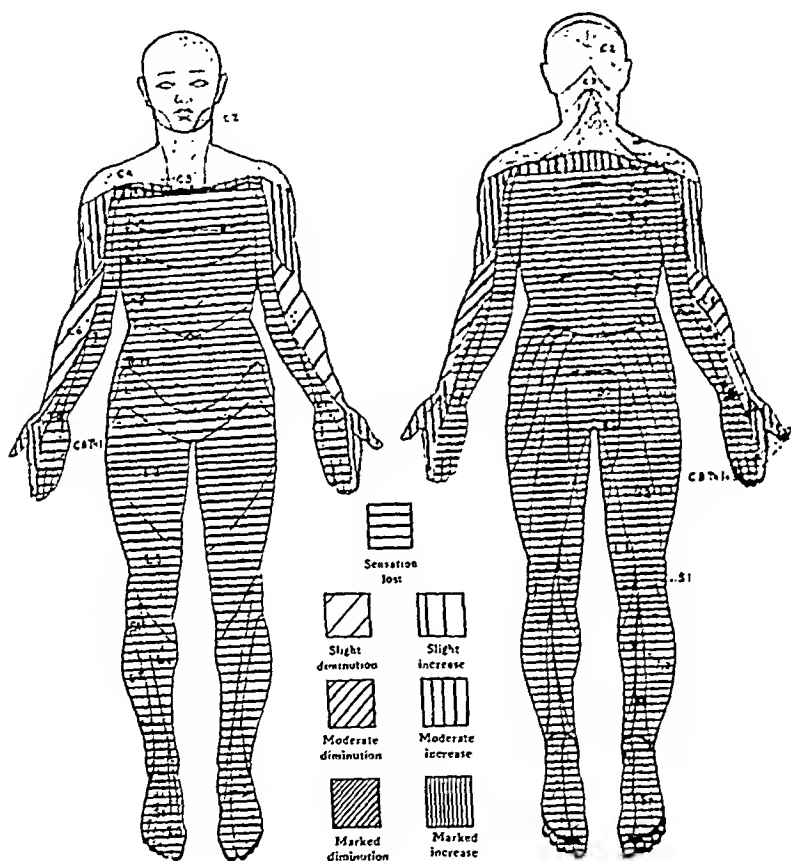


Fig. 6 (case 2).—A diagram showing the cutaneous sensory disturbances in a patient with an intramedullary tumor at the level of the ninth thoracic segment.

the cord appeared to be swollen and covered by enlarged tortuous vessels (fig. 7 A). A small hypodermic needle attached to a syringe was introduced into the cord in the midline in an attempt to aspirate fluid from a possible cystic cavity, but none was encountered. The cord generally appeared to be greatly widened and pulsated but feebly. It was thought best not to explore further and not to incise the cord. The dura was left open and the rest of the wound was closed carefully in layers.

Postoperatively the patient had a rather stormy convalescence; however, the wound healed well and the patient was discharged to her home on May 19. Before

leaving the hospital she was given several high voltage roentgen exposures, and at the time of leaving for her home she was able to walk about with the aid of a cane.

The patient did extremely well for almost a year and a half, during which time she used a cane for twelve months and then for almost six months was able to walk without support. She returned to the hospital on Oct. 10, 1933, with a complaint of severe pain in the back and legs. She stated that she had felt very well until one month previously. The neurologic findings at this time were practically the same as on the first admission. The sensory level was now limited by

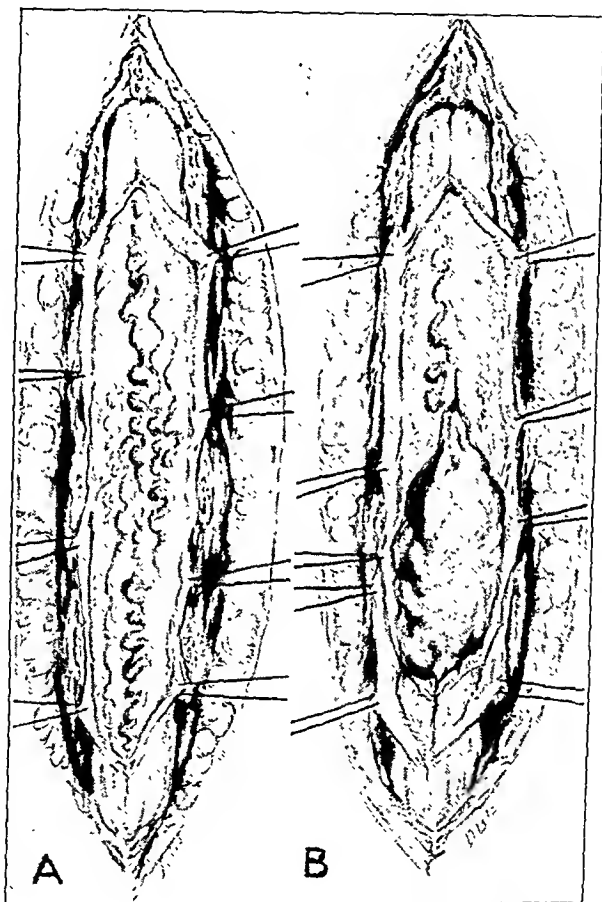


Fig. 7 (case 2).—*A* is a drawing showing the markedly swollen condition of the spinal cord with greatly enlarged vessels at the time of the first operation, and *B* is a drawing of the extrusion of an intramedullary tumor after midline incision of the spinal cord.

a zone of hyperesthesia from the sixth to the eighth dorsal segment, below which all forms of sensation were markedly diminished. The tendon reflexes in the lower extremities were very sluggish, and there were no pathologic reflexes. Examination of the spinal fluid revealed a markedly yellow fluid, and there appeared to be a complete subarachnoid block.

Pain in the legs and back became excruciating, and it was decided to reexplore the area previously examined in an effort to locate an intramedullary tumor. Our experience in the first case had furnished sufficient courage to make us feel that

incision of the cord might reveal a neoplasm amenable to surgical intervention. Accordingly, on October 26 an incision was made above the old operative scar beginning at the level of the fifth dorsal vertebra. The incision was carried down through the old operative wound in its entire length. At the level of the sixth dorsal vertebra the spinal cord appeared to be yellowish and swollen and felt cystic. A small incision was made in the midline of the spinal cord at the upper pole, and a small cyst was evacuated. At the lower end of this cyst at the level of the sixth dorsal vertebra a large grayish tumor presented itself. The overlying spinal cord was split in the midline to a depth of 1 mm., and the tumor gradually exposed. The neoplasm was gently elevated by means of silk traction sutures and was lifted from its bed from within the spinal cord (fig. 7 B). At the level of the tenth dorsal vertebra two large vessels were seen to be entering the tumor. These were caught with silver clips and divided. The laminae of the eleventh and twelfth dorsal vertebrae had to be removed before the tumor could be removed in its entirety. The wound was then carefully closed.

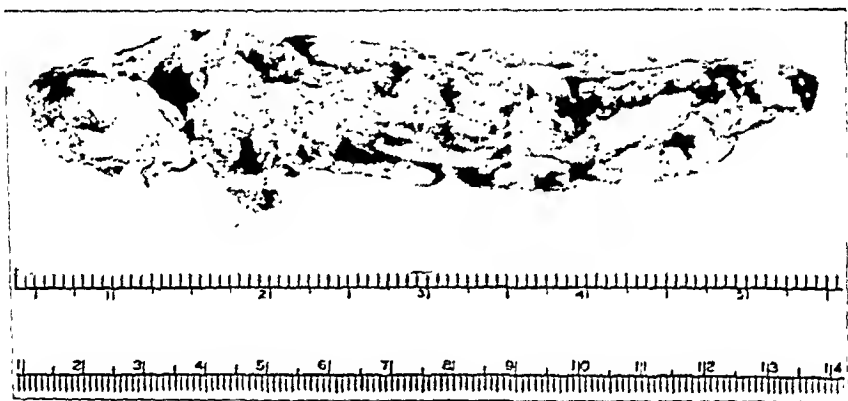


Fig. 8 (case 2).—An ependymal glioma from the thoracic portion of the spinal cord which extended from the sixth to the twelfth segment. It weighed 30 Gm. before fixation.

*Course.*—Postoperatively the patient had a very stormy course for several days and then appeared to be gradually improving. The lower extremities were markedly weak after the operation, with involvement of both sphincters. The sutures were removed on the tenth postoperative day. The temperature and pulse rate remained within normal limits throughout this period, but the patient complained continuously of severe pain in the back and vomited frequently. At this time the lower pole of the wound broke down and there developed a small cerebrospinal fluid fistula. Several attempts to repair the wound proved unsuccessful, and within a few days there developed the signs and symptoms of a meningeal infection with cervical rigidity and a high temperature. Supportive treatment proved to be of no benefit, and the patient died on December 11.

*Pathologic Examination.*—The tumor (fig. 8) measured 12.5 cm. in length and 2 cm. in diameter and weighed 30 Gm. shortly after removal and before fixation. It was somewhat cigar-shaped, being pointed at either end. It appeared to be encapsulated and presented numerous lobules of various size on its surface. The tissue was soft, reddish-gray, friable and mottled with hemorrhagic areas (fig. 9).

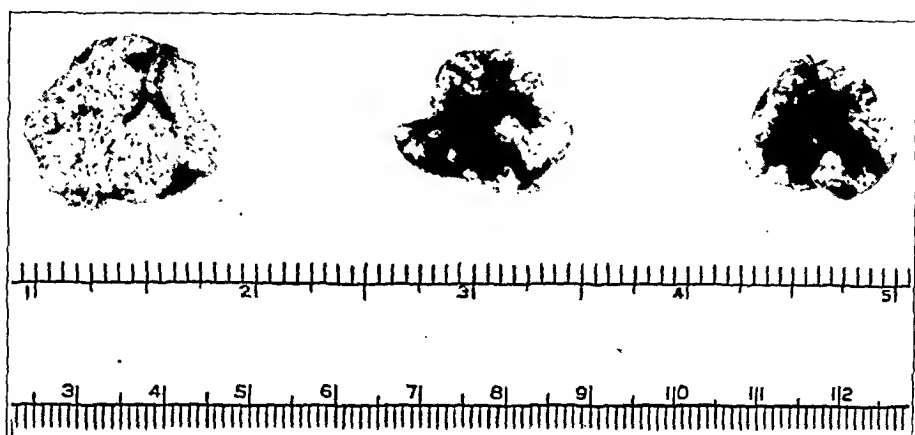


Fig. 9 (case 2).—Transverse sections of the tumor depicted in figure 8, showing marked vascularity.

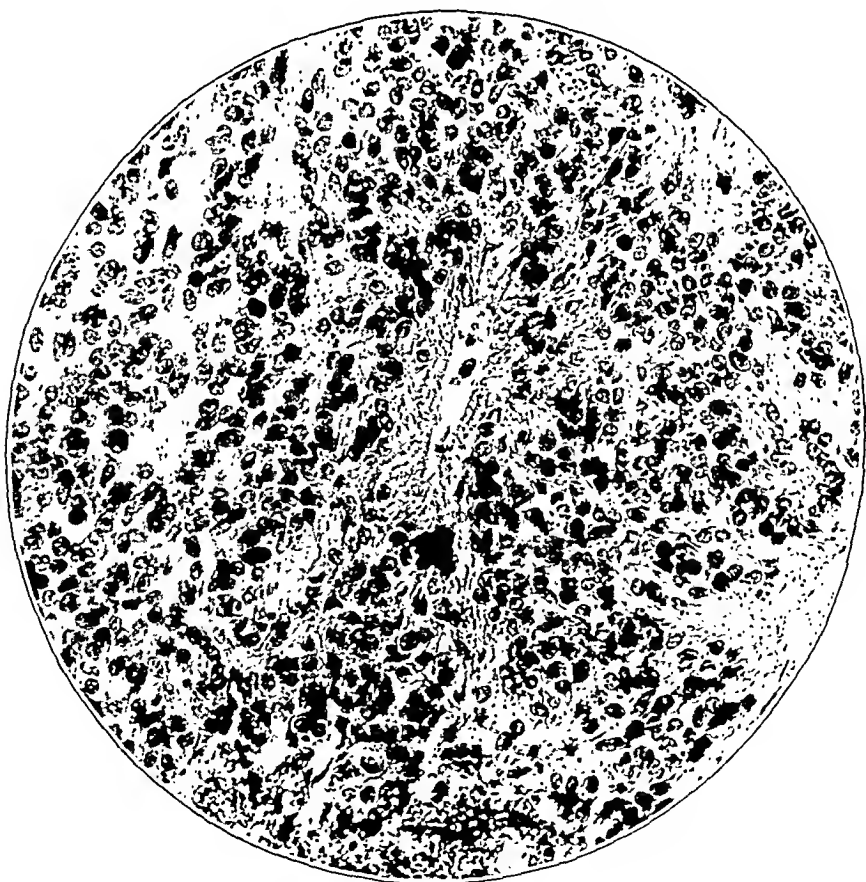


Fig. 10 (case 2).—A section of an ependymal glioma (ependymoblastoma), showing the tendency to form pseudorosettes about the blood vessels. Hematoxylin and eosin stain;  $\times 220$ .

*Histologic Examination.*—Examination revealed an ependymal glioma (fig. 10). The major portion of the tumor had a rather characteristic appearance with the cells tending to be arranged in pseudorosettes about a central blood vessel. However, some of the numerous larger cavities were lined with a condensed form of tissue representing embryonic ependyma. The tumor resembled that type of ependymal glioma known as an ependymoblastoma.

*Comment.*—Although the result in case 2 might well be termed a surgical disaster there are a few features concerned with the differential diagnosis as well as with the surgical technic that warrant careful study.

It is often extremely difficult to differentiate clearly between intramedullary and extramedullary tumors of the spinal cord. The absence of irritation of the posterior roots, a dissociated waistcoat type of sensory disturbance and a marked difference in the levels of the various sensory disturbances suggest intramedullary new growth. The presence of pain is not a commonly known symptom of intramedullary tumors, and its presence in case 2 was rather disconcerting. It has been explained as being due to associated adhesions of the arachnoid (arachnitis) by Foerster<sup>32</sup> in several of his cases of intramedullary tumor, and it is possible that pain in the roots can be produced by a tumor arising near the posterior horns. The duration of symptoms before surgical relief is sought can no longer be held as a criterion of intramedullary neoplasms. Kernohan<sup>4</sup> had three patients with intramedullary ependymomas, with histories of ten, thirteen and fourteen years' standing, respectively. As Spiller<sup>33</sup> said: "It is somewhat remarkable to think that the intramedullary group of tumors may have a longer duration of symptoms than the extramedullary and extradural tumors, particularly when one considers the small diameter of the spinal cord and the slight injury which is required to lead to complete paralysis." But with his usual sagacity Spiller suggested that "if the tissues studied were to be stained with the Bielschowsky silver stain, one might find that in many of these tumors axis cylinders passing directly through the tumor without being destroyed and therefore capable of functioning although under difficulty."

It is particularly important that scrupulous care be paid to effecting a tight closure of the wound so as to avoid a cerebrospinal fluid fistula, with a subsequent fatal infection. This complication is prone to develop in cases of this type when the dura is purposely left open and, as in case 2, may be the direct cause of a fatal issue. In one of the cases reported by Cairns and Riddoch<sup>31</sup> such a complication developed following operation but the patient finally recovered from the meningeal infection.

32. Foerster, O.: *Die Leitungsbahnen des Schmerzgefühls und die chirurgische Behandlung der Schmerzzustände*, Berlin, Urban & Schwarzenberg, 1927.

33. Spiller, W. G., in discussion on Kernohan, Woltman and Adson.<sup>4</sup>

## SUMMARY AND CONCLUSIONS

The ependymal glioma has come to be recognized as the common parenchymatous tumor of the spinal cord.

The surgical amenability of this type has not been sufficiently recognized when a large swollen spinal cord is exposed at operation and an intramedullary tumor is thought to be present.

This type of glioma tends to be encapsulated, offering a fair prognosis if successfully removed.

Surgical intervention employed in the treatment of such an intramedullary tumor includes, according to a consensus: (1) a wide laminectomy; (2) incision along the middorsal aspect of the cord with separation of the posterior columns; (3) removal of the tumor by careful blunt dissection with the aid of silk traction sutures; (4) leaving the dura open to provide sufficient decompression, and (5) careful tight closure of the wound.

Roentgen therapy following operation does not seem to be indicated, since this type of tumor appears to be benign.

Two cases of intramedullary spinal cord tumor of ependymal origin that have come to operation are described in detail.

# USE OF LOW TEMPERATURES IN CULTURE AND TRANSPORTATION OF SURGICAL MAGGOTS

S. W. SIMMONS, B.Sc., M.A.  
WASHINGTON, D. C.

Efficient retardation of development in the culture of surgical maggots permits the technician to maintain a constant supply with minimum effort. It is also one of the chief means by which cost of production can be lowered. Retardation is essential during the period of incubation in the tests of sterility, and it would be both economical and convenient if development could be restrained beyond this period. As subjection to low temperature has been the chief means of retardation, an investigation was made to determine its effect on maggots in storage.

A common practice of surgeons requiring a small or occasional supply of maggots is to purchase them from certain medical supply houses, and frequently shipments have to be made over long distances. Normally maggots develop rapidly, and if allowed to grow in transit they become too large for use in the wound. Their development has to be retarded in some way, therefore, during shipment. The usual method of preparing maggots for shipment is to pack the container next to ice in an insulated package. The package, however, is heavy and bulky and is expensive to prepare and mail. The greatest objection raised by surgeons using maggots for treatment has been the expense, many of their patients being dependent on charity. With a view to the reduction of expense, therefore, an investigation was also made of the efficiency of retardation by low temperature in transit.

Maggots used in this work were of the species *Lucilia sericata*; they were reared under the usual aseptic technic.<sup>1</sup>

## PROPORTION OF MAGGOTS THAT FEED AT VARIOUS TEMPERATURES

Both in storage and in transit, restraint of growth is of primary importance. Tests were therefore conducted to determine the proportion

---

From the Division of Insects Affecting Man and Animals, Bureau of Entomology and Plant Quarantine, United States Department of Agriculture.

1. Robinson, W.: Improved Methods in the Culture of Sterile Maggots for Surgical Use, *J. Lab. & Clin. Med.* **20:77** (Oct.) 1934. Simmons, S. W.: Sterilization of Blowfly Eggs in the Culture of Surgical Maggots for Use in the Treatment of Pyogenic Infections, *Am. J. Surg.* **25:140**, 1934.



of maggots that feed under various temperatures which might be chosen for the production of retardation.

Maggots of surgical size (from 4 to 6 mm. long) were removed from their food and subjected to the temperatures shown in table 1. They were then placed on colored food of the same temperature and returned to the refrigerator. Thus no feeding occurred except under controlled conditions. After approximately twenty-four hours all living specimens were examined microscopically for the presence of food in the alimentary tract.

The colored food was prepared by making a solution of normal beef blood serum and adding enough safranin to produce a deep red. After being mixed, the food was coagulated by heating and placed in the food bottles for autoclaving. Even slight feeding was detected in the intestinal tract, and tests proved that maggots fed readily on this food.

Observations indicated that there was feeding as long as activity persisted. Little feeding occurred at 4 C. (39.2 F.); however, while at from 8 to 9 C. (46.4

TABLE 1.—*Relation of Temperature to the Number of Maggots that Fed*

Temperature, Degrees		Number of Maggots Used	Maggots That Fed	
C.	F.		Number	Per Cent
4 - 6	39.2 - 42.8	381	17	4.4
8 - 9	46.4 - 48.2	62	33	53.2
10 - 11	50 - 51.8	268	216	80.6
20 - 21	68 - 69.8	198	195	98.5
27 - 29	80.6 - 84.2	109	107	98.2

to 48.2 F.) 53.2 per cent of the maggots fed (table 1). When the temperature was increased to 10 or 11 C. (50 or 51.8 F.), the proportion was increased to 80.6 per cent. Almost all the maggots (98.5 per cent) fed when a temperature of 20 C. (68 F.) was reached. The quantity of food consumed increased, of course, with the temperature.

#### GROWTH OF MAGGOTS AT VARIOUS TEMPERATURES

In tests already mentioned, 53.2 per cent of the maggots fed at a temperature of from 8 to 9 C. (46.4 to 48.2 F.). The amount of feeding, however, was negligible. The actual amount of growth, therefore, and not merely the indication of feeding, is the criterion to be used in establishing a temperature suitable for retardation. Tests were conducted to determine this temperature.

Maggots were taken from their food (composed of dehydrated liver, agar, yeast and water) and washed with distilled water for one minute to remove particles of food. The surface water was removed by allowing the maggots to crawl over filter-paper for four minutes. They were then counted, weighed and placed in the refrigerator until chilled to storage temperature. After this they were placed on fresh food of the same temperature, returned to the refrigerator and allowed to feed for seventy-two hours. This period was chosen because it is that for which

the cultures used in the sterility tests are incubated before the maggots are released and because it represents about the average time required for maggots in transit. Growth during storage was determined by removing the specimens and washing and weighing them as before. Four tests with 100 maggots each were made for each range of temperature indicated in table 2.

At a temperature of from 10 to 11 C. (50 to 51.8 F.) the increase in growth, namely, 23.4 per cent of the prestorage weight, can be tolerated without materially shortening the period of feeding of the maggots after implantation in wounds. A temperature of from 13 to 14 C. (55.4 to 57.2 F.) caused an increase of 90.7 per cent in weight. A higher temperature is, therefore, unsatisfactory, as maggots showing an increase in weight beyond 23.4 per cent would be excessively large after storage and would have only a short period of feeding in the wound.

On the basis of these tests, a maximum effective temperature was fixed at 12 C. (53.6 F.) as the highest temperature that can be tolerated in the retardation of maggots.

TABLE 2.—*Relation of Temperature to Growth of Surgical Maggots During Seventy-Two Hours*

Temperature, Degrees		Mean Prestorage Weight per Specimen, Mg.	Mean Poststorage Weight per Specimen, Mg.	Mean Gain in Weight per Specimen During Storage, Mg.
C.	F.			
10 - 11	50 - 51.8	4.7	5.8	1.1
13 - 14	55.4 - 57.2	4.3	8.2	3.9
15 - 16	59 - 60.8	4.1	16.9	12.8
20 - 21	68 - 69.8	6.5	22.4	15.9

#### EFFECT OF RETARDATION BY LOW TEMPERATURE ON VIABILITY OF MAGGOTS

The mortality of maggots during storage is of much importance. Although low temperature is used extensively as an agent to induce retardation it also causes a high mortality. If a high death rate during retardation could be avoided, maggots could be held in an arrested state for several days. This would considerably reduce the expense of production and, by permitting long distance shipments, would make surgical maggots more available to remote districts. Tests were conducted to determine whether the death rate is so great as to make the continued use of this method of retardation inadvisable.

The maggots used in these tests were reared on the nutrient food already mentioned, under the usual aseptic precautions; when they reached surgical size they were stored in the same kind of food at a temperature of from 5 to 6 C. (41 to 42.8 F.) for periods ranging from one to six days.

The period of mortality may be divided into two phases: (1) the time from the hatching of the eggs until the maggots are implanted in the wound and (2) the period after implantation. Maggots that survive cold storage are not necessarily able to resume feeding when placed in the wound, and obviously they would be

of no clinical value if unable to feed. As a test of the tolerance of maggots to cold storage, it was therefore required that they should be able to feed and grow when placed on necrotic tissue.

Cold storage of surgical maggots caused an extreme mortality (table 3). After two days' storage, which is the usual period of retardation during the sterility tests, the mortality was 66.6 per cent. The fact that two thirds of the maggots were lost during this period of storage is significant, and as the death rate increased rapidly each day, the futility of prolonged storage is evident. When maggots were retarded for six days the mortality was almost 100 per cent, while maggots reared under similar conditions but not subjected to cold had a mortality of only about 19 per cent.

TABLE 3.—*Mortality of Surgical Maggots Resulting from Cold Storage at from 5 to 6 C. (41 to 42.8 F.)*

Time in Storage, Days	Number of Experiments Conducted	Number of Maggots Used	Number That Survived Storage	Number Able to Resume Feeding	Percentage of Mortality*
1	7	3,006	2,655	1,104	63.3
2	6	2,764	1,650	922	66.6
3	6	2,823	1,112	604	78.6
4	5	2,183	781	397	81.8
5	4	985	391	119	87.9
6	2	448	55	7	98.4

\* The number includes those that were dead when removed from storage and those not able to resume feeding.

The enormous death rate of surgical maggots caused by cold storage often escapes detection, and the fact that about one half of those which do survive storage are unable to resume feeding is still more likely to be overlooked. Fortunately, another method of retardation is possible<sup>2</sup> which eliminates the use of low temperature. This method considerably reduces the expense and labor involved in the culture of maggots and, by lowering the mortality of the maggots, increases their therapeutic value.

#### RETARDATION OF MAGGOTS IN TRANSIT BY LOW TEMPERATURE

When maggots are purchased shipment by mail is usually necessary and the essential retardation during transit has been attempted chiefly by packing in iced containers.

*Method.*—To test the efficiency of this method, determinations were made of the temperatures within the packages, and these temperatures were compared with the maximum effective temperature of 12 C. (53.6 F.). Two standard types of packages were prepared for shipment in the usual way. One type was a cylindric

2. Simmons, S. W.: Adequacy of Nutritional Retardation in the Culture of Sterile Maggots for Surgical Use, this issue, p. 1024.

carton having metal ends and insulated with corrugated paper and cellulose. Some of these cartons were placed on end and others on their sides, as in transit. The second type was a rectangular cardboard box filled with ground cork for insulation. Ice was supplied in the usual way, by freezing water in tin cans of a capacity of 245 cc. Each bottle of maggots, with the usual small quantity of nutrient food, was packed next to the can of ice.

The temperature of each bottle after packing was determined with a four point multiple thermocouple placed in the bottle in the following position: Point 1, in contact with the base of the cotton plug; point 2, suspended in mid-air between the base of the bottle and the plug; point 3, fastened to the inner wall of the bottle on the same level as point 2, and point 4, inserted into the food.

Readings were taken at one-half hour or one hour intervals, and tests were conducted under the shipping conditions of both summer and winter.

*Tests Under Summer Conditions.*—The tests were made in July with atmospheric temperatures (chart 1) of from 30 to 33 C. (86 to 91.4 F.). The only

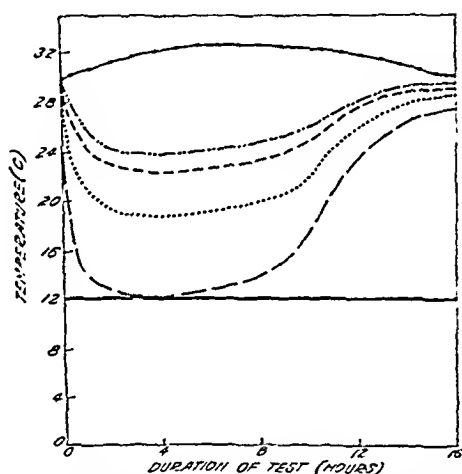


Chart 1.—Temperatures in cylindric iced shipping package under summer conditions. In this chart and in the accompanying charts, the solid straight line represents the maximum effective retardation-inducing temperature; the solid curved line with crosses, the temperature of the air; the line of dash and dots, the temperature of point 1; the line of short dashes, the temperature of point 2; the line of medium dashes, the temperature of point 3, and the line of long dashes, the temperature of point 4.

temperature in the cylindric iced package low enough to produce successful retardation was recorded by point 4, which was inserted in the food next to the ice. This temperature was 12.1 C. (53.8 F.), but it lasted only about one hour. The temperatures in the upright and prone packages were similar, and their averages were taken. About the cotton plugs it was always warmest, the mean maximum temperature being 24 C. (75.2 F.). In sixteen hours the mean minimum temperature was 27.5 C. (81.5 F.), at which temperature maggots are always active and feeding. Thus it is evident that under summer conditions practically no retardation of the maggots is accomplished by this method.

The temperatures in the rectangular package were more uniform (chart 2) but higher. The food was always warmest and the wall of the jar coolest, but the

difference in temperature was only about 3 C. (5.4 F.). The mean minimum temperature was 18.5 C. (65.3 F.), which was not sufficiently low to produce dormancy of the maggots.

These tests were purposely conducted under the most unfavorable atmospheric conditions of summer, so that the adequacy of retardation by low temperature for the conditions of this season and of tropical countries might be determined.

*Tests Under Winter Conditions.*—Winter temperature was obtained by placing the package in a mechanical refrigerator maintained at 20 C. (68 F.). This tem-

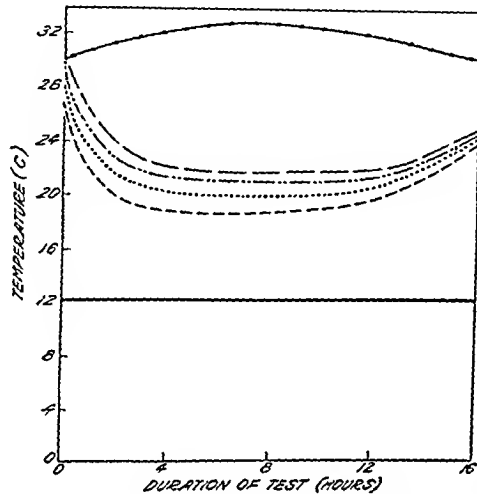


Chart 2.—Temperatures in rectangular iced shipping package under summer conditions.

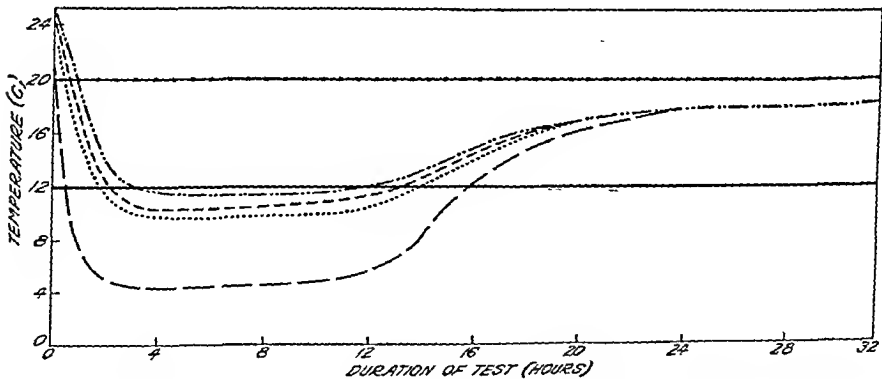


Chart 3.—Temperatures in cylindric iced shipping package under winter conditions.

perature was chosen as that usually encountered by maggots in mail-coaches and post-offices. The insulation of the bottle prevents chilling when the package is exposed for brief periods outside.

Under these conditions the temperatures in the bottles were both lowered and prolonged. In the cylindric containers the temperatures bore a parallel relationship to those under summer conditions. The lowest temperature, 4.5 C. (40.1 F.), was reached in the food (chart 3). By the first hour this had risen to 7.5 C. (45.5 F.); no appreciable increase occurred before the end of fourteen hours. A uniform temperature of 17.5 C. (63.5 F.) was recorded throughout the bottle in twenty-three

hours, and it was approximately that of the surrounding atmosphere in thirty hours. All portions of the bottle were sufficiently cooled to produce a successful degree of dormancy, but only for fifteen hours. The duration of the retardation-inducing temperature in the warmest portion of the bottle was only about eight hours, and, as is shown later in this paper, it is naturally this portion in which the maggots tend to cluster.

In the rectangular package the temperatures of the bottle were lower and rose more slowly, of course, than under summer conditions. The variation in temperature between the different parts of the bottle (chart 4) was only 2.5 C. (4.5 F.), and all temperatures had the same relationship to each other as those under summer conditions. In this type of package the temperatures also fell and rose more slowly than in the cylindric container. The lowest temperature was recorded on the side adjacent to the ice. There an effective retardation-inducing temperature was maintained for eighteen hours, while in the food the time of retardation was reduced to fourteen hours. A successful degree of retardation of the maggots was obtained in all portions of the bottle, but the low temperature did not persist long enough to permit successful long distance shipping.

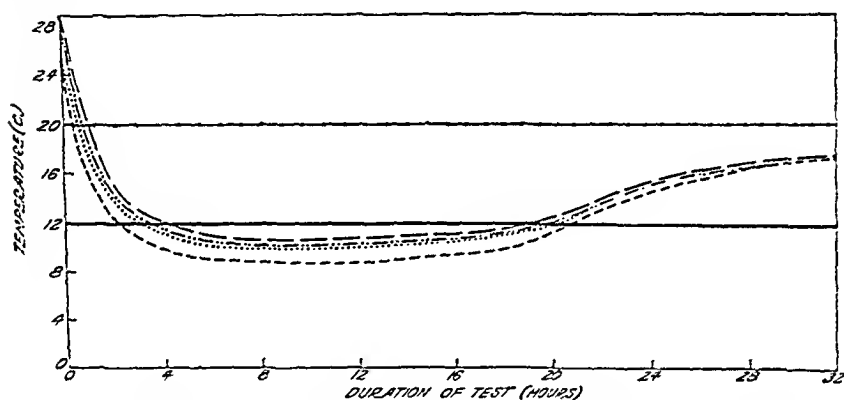


Chart 4.—Temperatures in rectangular iced shipping package under winter conditions.

#### EFFECT OF TEMPERATURE GRADIENT ON MIGRATION OF MAGGOTS

As the temperatures in a bottle of maggots varied when placed next to ice, it was assumed that the specimens would migrate to the warmest part. The lower temperatures would thus be ineffective. Tests were therefore conducted to determine this point.

Bottles containing food and maggots were placed on cans of ice, and the activity of the maggots was observed as the temperature fell.

In each case the maggots began to wander from the food when it was chilled to 18 C. (64.4 F.). They fed readily, however, at this temperature if no higher one was available. Further chilling to 14 C. (57.2 F.) caused most of them to leave the food and cluster in the warmer parts near the plug, and they returned to the food only when it had become warm. In charts 1, 2, 3 and 4, it is shown that this migration considerably reduced the effectiveness of the retardation-inducing temperature during shipment. On the basis of this migration, retardation lasted only about fourteen hours under the most favorable conditions (chart 4).

The foods so far in use, unfortunately, tend to run to the warmer parts of the bottle, thus becoming available to the maggots and promoting rapid growth during most of the period in transit. The tendency, therefore, is toward either overgrowth or excessive mortality, either of which prevents satisfactory utilization of this method.

TEMPERATURE AT WHICH MAGGOTS FREEZE

Tests to determine the temperatures at which the maggots would freeze were made with a thermocouple by the contact method, as devised by Robinson.<sup>3</sup> The specimens used were of the typical surgical size (from 4 to 6 mm. in length). A summary of the data is given in table 4.

As freezing cannot occur until the undercooling point is reached, it is seen that freezing is impossible under ordinary conditions of cold storage.

TABLE 4.—*Undercooling and Freezing Points of Surgical Maggots*

	Undercooling Points, Degrees		Freezing Points, Degrees	
	C.	F.	C.	F.
Maximum temperature.....	—14.6	7.9	—7.2	19.8
Minimum temperature.....	—10.0	14.0	—4.1	25.0
Average temperature.....	—11.4	12.9	—5.5	23.9

COMMENT

The customary method of retardation of surgical maggots by low temperature is inefficient. After two days of storage at from 5 to 6 C. (41 to 42.8 F.) only one third of the maggots were able to resume feeding under conditions similar to those in the wound; a period of retardation of this length is necessary during the sterility tests. After an additional storage of four days, as would be required during shipment or when surplus maggots were held on hand, less than 2 per cent fed.

The use of iced containers for maggots in transit is not only expensive but inefficient. In summer no significant degree of retardation is obtained by ice alone. In winter a certain degree of retardation is possible. This may last as long as from eight to eighteen hours but this time is not sufficient to permit successful shipping for long distances.

At temperatures between 15 and 21 C. (59 and 69.8 F.) maggots gained about 75 per cent in weight during seventy-two hours. This range of temperature is always available to them under shipping conditions in summer and during most of the time under conditions in winter.

Since the completion of this investigation, one medical supply house has used a larger ice can (with a capacity of 445 cc.), which somewhat prolongs the duration of the retardation-inducing temperature. However, if the period were to be increased three times, there would be only

3. Robinson, W.: Determination of the Natural Undercooling and Freezing Points in Insects, J. Agric. Research 37:749, 1928.

about two days of retardation under the most favorable conditions, and, as already shown, only one third of the maggots would be able to resume feeding. The increased quantity of ice also adds considerably to the weight of the package and the cost of mailing.

In the cases in which packing with ice has been employed with apparent success, the results have been largely due to the fact that the maggots' food was sufficiently low in nutrient value to aid greatly in the retardation.

In view of the inadequacy of retardation by low temperature a more satisfactory method is desirable. In an accompanying paper<sup>2</sup> a method of effecting retardation by nutritional means alone is described. With this new method the disadvantages are less than with cold storage and the period of successful retardation is considerably longer.

#### SUMMARY

A study was made of the value of retardation of surgical maggots by low temperature. The work included an investigation of the proportion of maggots that feed at various temperatures, showing that over 75 per cent of the maggots fed at 10 C. (50 F.).

The size of the maggots increased 23.4 per cent when they were stored for seventy-two hours at from 10 to 11 C. (50 to 51.8 F.), while at from 13 to 14 C. (55.4 to 57.2 F.) the increase was 90.7 per cent. Any temperature higher than 12 C. (53.6 F.) was found to stimulate too rapid growth and development for successful retardation of the maggots.

The mortality of maggots in storage at low temperatures is extremely high. Even when stored for forty-eight hours at from 5 to 6 C. (41 to 42.8 F.), only one third were able to resume feeding, and the mortality was nearly 100 per cent after six days. This high rate necessitates the early use of the maggots and prohibits their retention for later use when not needed immediately.

As this method of retardation is used in shipping maggots by mail, its efficiency has been investigated from that standpoint. Tests were conducted under conditions of both summer and winter and it was found that the temperature was not sufficiently low over a long enough period to prevent growth and development during transit.

The temperature in a bottle of maggots packed next to ice is not uniform throughout, and maggots migrate to the warmer portions. The retarding effect of the lower temperature is therefore lost.

If a sufficiently low temperature could be maintained throughout the period of transit, most of the maggots would be killed, as they are not tolerant of such conditions.

Reference is made to an investigation in which a method has been devised for the nutritional retardation of maggots.



# ADEQUACY OF NUTRITIONAL RETARDATION IN CULTURE OF STERILE MAGGOTS FOR SURGICAL USE

S. W. SIMMONS, B.Sc., M.A.  
WASHINGTON, D. C.

Retardation is a necessity and a convenience in the production of maggots for surgical use. It is an essential step in the process because during the tests of sterility, which are made on all maggots, the growth of the maggots must be restrained; otherwise they become too large for use in wounds. It is also essential during long distance shipments. Retardation is a convenience, as it permits the holding over of maggots not needed at the time.

Low temperature is at present the chief means used to produce retardation, but a recent investigation<sup>1</sup> has shown this method to be injurious, chiefly because it destroys a large percentage of the maggots. In view of the need of a more efficient method, experiments were conducted on retardation by nutritional means.

The maggots used were those of the species *Lucilia sericata*; they were reared under the usual aseptic technic.<sup>2</sup> All cultures were kept in a cabinet maintained at 27 C. (80.6 F.).

## THE RETARDATION-INDUCING FOOD

*Standards of a Retardation-Inducing Food.*—There are various foods by which the growth of maggots can be retarded, but most of these cause considerable mortality or lack some of the essentials to be enumerated.

A good food for this purpose should conform to the following standards: (1) The food must permit only a slow rate of growth; (2) it must at the same time retard development in conformity with the slow rate of growth; (3) the mortality during retardation should be slight; (4) the food should be nutritionally homogeneous throughout to allow uniform growth of all the maggots; (5) it should be of the proper consistency to permit free activity of the maggots; (6) it should permit the easy removal of the maggots; (7) it should resist drying; (8) the

---

From the Division of Insects Affecting Man and Animals, Bureau of Entomology and Plant Quarantine, United States Department of Agriculture.

1. Simmons, S. W.: Sterilization of Blowfly Eggs in the Culture of Surgical Maggots for Use in the Treatment of Pyogenic Infections, *Am. J. Surg.* **25**:140, 1934.

2. Robinson, W.: Improved Methods in the Culture of Sterile Maggots for Surgical Use, *J. Lab. & Clin. Med.* **20**:77, 1934. Simmons.<sup>1</sup>

food materials should be accessible to the laboratory; (9) the food should be simple, cheap and easy to prepare.

*Preparation.*—A wide range of foods was tested. The one which proved to be the best and simplest is prepared as follows: evaporated milk (fresh), 1 part;<sup>3</sup> distilled water, 7 parts; agar, 1.5 per cent.

The milk and water are mixed; the agar is then added, and the mixture is cooked in a double boiler for about twenty-five minutes. It should be poured into the food bottles<sup>4</sup> while hot. Ordinarily, from 12 to 15 cc. is used in each bottle. The proportion of milk and water is sufficiently nutritious to sustain the larvae without allowing material growth and development. Some latitude in concentration is tolerated, however, any ratio of from 5 to 7 parts of water to 1 part of milk being suitable. Solutions of less than 1 part of milk to 7 parts of water are not satisfactory, as the milk tends to settle out during autoclaving so that it is overlaid with clear agar. This condition is not desirable, as newly hatched larvae should have immediate access to the milk.

A 1.5 per cent solution of agar gives a jelly-like consistency which is sufficiently soft to allow free activity of the maggots and yet is firm enough to prevent running. The agar acts as a hydrophilic colloid and thus prevents undue desiccation of the food. This action is important, as lack of moisture is detrimental to the maggots. The specimens are easily removed from the food by pouring sterile water into the bottle and stirring with an applicator, after which the maggots are strained out. If cold water is used the maggots are subdued so that they will not escape from the wound before the cage is applied.

#### GROWTH AND DEVELOPMENT OF SURGICAL MAGGOTS ON RETARDATION-INDUCING FOOD

The rate of development as well as of growth must be reduced by the retarding agent. Although the two functions usually occur simultaneously, they can be separated. If growth alone were arrested and development continued, the maggots would be useless surgically after about five days, even though they were no larger than normal surgical maggots, for they would not feed in the wound. On the other hand, if growth were well advanced before implantation, one of the outstanding activities of the maggots, namely, the removal of necrotic tissue in feeding,<sup>5</sup> would be correspondingly reduced.

In the evaluation of the food it was therefore necessary to determine the rate of growth and development of maggots during various periods of retardation. This was done by making measurements of size and

---

3. The proportion used was based on the usual commercial concentration, which is about twice that of whole milk.

4. Robinson, W., and Simmons, S. W.: *Surgical Maggots in the Treatment of Infected Wounds: Recent Apparatus and Methods in Maggot Production and Research*, J. Lab. & Clin. Med. **19**:339, 1934.

5. Robinson, W., and Norwood, V. H.: *The Role of Surgical Maggots in the Disinfection of Osteomyelitis and Other Infected Wounds*, J. Bone & Joint Surg. **15**:409, 1933.

determinations of instar every twenty-four hours until the period of successful retardation had passed.

It was found that limitation of both growth and development could be effected (table 1) without allowing the maggots to grow beyond the recommended surgical size of from 4 to 6 mm. in length. On the eighth day the average length of the maggots was only 6.3 mm. Then followed a period of slight shrinkage. While a small percentage of the maggots developed into the third instar after one week, the majority remained in the second instar throughout the period of retardation. As feeding takes place chiefly in the third instar, it is evident that the maggots would have four or five days for feeding after implantation.

These tests were conducted with the usual number (from 500 to 700) of sterile maggots in each bottle. When an extremely small number is used, however, growth tends to be more rapid.

TABLE 1.—*Growth and Development of Maggots on Retardation-Inducing Food*

Age of Maggots from Sterilization of Eggs, Days	Length, Mm.	Percentage of Maggots in Each Instar		
		First	Second	Third
1.....	2.0	100	..	..
2.....	2.8	60	40	..
3.....	4.3	..	100	..
4.....	5.3	..	96	4
5.....	5.6	..	96	4
6.....	6.0	..	88	12
7.....	6.0	..	76	24
8.....	6.3	..	70	30
9.....	6.2	..	72	28*
10.....	6.0	..	64	36

\* On the ninth day slightly fewer maggots appeared in the third instar than on the eighth day. This may be attributed to the incidental results of the random sampling.

#### MORTALITY DURING RETARDATION

Two periods of mortality may be considered as a result of retardation: (1) the time from the hatching of the eggs to the implantation in the wound, during which the maggots have the retardation-inducing food and (2) the interval after transference to the wound. The second period will be discussed in the following section.

In determining the mortality during the first period, a series of bottles of sterile specimens was prepared, each bottle containinig equal numbers of eggs by weight.<sup>4</sup> On the third day of retardation the maggots from one third of these bottles were counted; the others were counted on the sixth and ninth days, respectively. The average mortality for each series is shown in a succeeding paragraph, but a certain degree of fluctuation occurred within the series.

The total number of live specimens from the three day series was 861; no dead maggots were seen. With retardation by low temperature for three days, however, there was a mortality of 60 per cent.<sup>6</sup> On the sixth day the total number

6. Simmons, S. W.: Use of Low Temperatures in the Culture and Transportation of Surgical Maggots, this issue, p. 1014.

of live maggots was 762, showing a mortality of 11.5 per cent due to nutritional retardation as compared with that of 87 per cent due to retardation by low temperatures. The total number of maggots in the nine day series was 727, which is a decrease of 15.6 per cent from that in the three day series. With retardation by low temperature all the maggots were killed in nine days.

#### EFFECT OF NUTRITIONAL RETARDATION ON FEEDING IN THE WOUND

As retardation is an unnatural process, unfavorable effects which might manifest themselves after implantation of the maggots in the wound were to be considered. If maggots were to die prematurely in the wound or fail to feed vigorously, their therapeutic value would, of course, be correspondingly reduced. It was therefore essential to determine (1) the proportion of maggots that would resume feeding when transferred to the necrotic tissue, (2) the amount of tissue consumed and (3) the length of time the maggots would feed. These points are discussed in the following subsections.

The laboratory tests described in this section were supplemented by clinical observations made on patients at the George Washington University Hospital, the Gallinger Municipal Hospital and the Emergency Hospital, in which nutritionally retarded maggots were supplied for the purpose. The results were confirmed in numerous instances by surgeons in various parts of the United States.

*Technic.*—Twenty-seven bottles of sterile maggots were prepared, and as a check the tests were conducted in two series. After the maggots were 3 days old, a known number of several hundred from each of a number of bottles was transferred to a definite quantity of necrotic beef. This procedure was repeated with maggots 5, 6, 7, 8 and 9 days old. The containers of meat were placed on sand, which was examined each day for maggots. The meat was also examined for dead maggots. Any maggots left in the meat after five days of feeding were removed and counted. By this method the proportion able to resume feeding and the length of the period of feeding were determined.

In each series additional containers of meat, without maggots, were prepared as controls to determine the natural loss of weight by desiccation. The average weight of meat per container was 144.2 Gm., and the maximum variation between individual containers did not exceed 1.4 Gm. This was true of the containers both with and without maggots. The loss in weight averaged about 37 per cent, and, with this factor known, the quantity of tissue consumed by the larvae could be determined. It is probable that the amount of desiccation from the two groups of food differed slightly, owing to the activity of the maggots in the one group. This variation, however, should have little practical bearing on the results obtained.

*Proportion of Maggots Able to Resume Feeding.*—Practically no injury to the larvae was evident after three days of nutritional retardation. This is shown by the fact that 79.6 per cent of the maggots that hatched developed to maturity when placed on necrotic tissue (table 2).

This proportion is as great as the number which ordinarily mature when reared on nutrient cultural food. When retarded by a low temperature of from 5 to 6 C. (41 to 42.8 F.) for three days, however, only 21.4 per cent were able to resume feeding.<sup>6</sup>

There was little additional mortality after five days of retardation, as 76.6 per cent of the maggots developed to maturity when placed on necrotic tissue. This number is in striking contrast to that of maggots retarded for the same length of time by low temperature, of which only 12.1 per cent were able to resume feeding. After six days this number was reduced to 1.5 per cent,<sup>6</sup> while with nutritional retardation 70 per cent of the maggots were able to continue feeding.

After seven days of retardation a considerable drop occurred in the percentage of maggots which were able to feed. On the basis of the

TABLE 2.—*Effects of Nutritional Retardation and Retardation by Low Temperature on the Number of Maggots Able to Resume Feeding and on the Amount of Tissue Removed\**

Retardation Period, Days	Percentage of Maggots Able to Feed		Necrotic Tissue Consumed per Hundred Maggots, Gm.	
	Nutritional Retardation	Retardation by Low Temperature	Nutritional Retardation	Retardation by Low Temperature
3.....	79.6	21.4	6.4	1.5
5.....	76.6	12.1	6.0	1.0
6.....	70.0	1.5	5.1	0.1
7.....	51.8	0.0	4.8	No observation
8.....	45.3	0.0	3.8	No observation
9.....	28.1	0.0	2.1	No observation

\* The results are based on a definite number of maggots at hatching.

number that hatched, 51.8 per cent were able to feed and develop to maturity, while after eight days the number was reduced to 45.3 per cent. This proportion is twice as great, however, as the number which were able to feed when retarded for only three days by low temperature. It is not possible to keep maggots under low temperature in a condition in which they will feed after seven days.

At the end of nine days 28.1 per cent developed to maturity when given the proper food. The mortality incurred after this time is often compensated for by the convenience of holding over sterile maggots for future use.

The usual mortality in a bottle of maggots is extremely difficult to detect and therefore frequently overlooked. Because dead maggots are sometimes moved about or obscured from view by the activity of living ones, the assumption is often made that they are all alive. On making actual counts, however, it is frequently found that a large number are dead. This is especially true if the maggots have just died and discoloration has not yet taken place. After retardation by low temperature or after prolonged nutritional retardation many maggots may die and

disintegrate. The diminution in the number of live maggots in this manner is not readily noticeable, as even 100 or 200 live maggots in a bottle appear to be a great number.

*Amount of Necrotic Tissue Removed.*—In the final analysis of the effect of retardation on the therapeutic value of maggots, the quantity of necrotic tissue which they can remove from the wound is of primary importance. A unit of 100 newly hatched maggots removed 6.4 Gm. of tissue after three days of nutritional retardation (table 2). In reality, 100 living maggots would remove more than this, but as there is a slight mortality through retardation, less than this number were available. The usual osteomyelitic wound may require an implantation of 500 maggots, and in this case 32 Gm. of necrotic tissue would be removed. On the other hand, 500 specimens retarded by low temperature for three days, which includes the period during the tests of sterility, were able to remove only 9 Gm. of tissue.

TABLE 3.—*Effect of Nutritional Retardation on Length of Feeding Time of Maggots on Necrotic Tissue*

Retardation Period, Days	Percentage of Maggots Ceasing Feeding After				
	Two Days	Three Days	Four Days	Five Days	More Than Five Days
3.....	0.0	4.2	91.5	0.4	0.9
5.....	0.0	5.1	91.0	2.5	1.4
6.....	0.08	14.4	75.4	5.2	1.9
7.....	0.4	4.1	62.7	22.0	10.8
8.....	0.2	7.1	29.4	39.0	24.3
9.....	0.0	3.1	29.1	39.5	28.3

After five days the amount consumed per hundred maggots was 6 Gm.; after six days, 5.1 Gm., and after seven days, 4.8 Gm. Even after eight days over one half of the potential feeding capacity of the maggots was still available. It is interesting to note that even after nine days the therapeutic value of the maggots was still considerable, while with retardation by low temperature the value practically ceased to exist after three days.

On account of the excessive serous exudation of the wound which is stimulated by the presence of the maggots, a certain amount of necrotic tissue is discharged from the wound with the drainage. This could not be determined by the method used. The data shown, therefore, probably do not represent the maximum amount of tissue removed.

*Duration of Feeding in the Wound.*—The length of time that surgical maggots are usually allowed to feed in the wound is from three to four days. A few still feed if left for five days. It is shown in table 3 that nutritionally retarded maggots were able to feed for the required period, and this has been confirmed by numerous clinical tests. The duration

of feeding and the large number that survive under this method increase the therapeutic value of such maggots.

#### APPLICATION OF NUTRITIONAL RETARDATION

*In the Laboratory and Hospital.*—Both labor and expense in maggot culture can be reduced by nutritional retardation. This method restrains the growth and development of maggots during the sterility tests with the minimum amount of injury. It also permits maggots to be held for several days after they are ready for use, which eliminates the need of sterilizing eggs daily to maintain a continuous supply of specimens, since sterilization twice a week is sufficient.

After the maggots are received at the hospital the surgeon is frequently unable to use them promptly; it is therefore convenient and economical to be able to hold them over until needed. This can be done when maggots are retarded nutritionally but not when they are retarded by low temperature.

*During Transit.*—When only a few maggots are required, they are usually purchased from certain pharmaceutical supply houses, and frequently they have to be shipped for long distances. Retardation during transit has been attempted chiefly by packing in ice, but this method has been proved inefficient.<sup>6</sup> Experiments have been conducted on nutritional retardation during transit, not only in the laboratory but in actual practice. Surgical maggots were shipped from Washington, D. C., to New York, Pennsylvania, Ohio, Iowa, North Dakota, Oregon, California, Texas and Alabama. The time spent in transit varied from three to eight days, and in every instance but one<sup>7</sup> the maggots were reported to be alive and active on arrival and able to feed for four or five days after being transferred to necrotic tissue. Maggots have also been kept in the laboratory in which this investigation was made for a week or longer and then used in human wounds at hospitals in Washington with excellent results.

When this method of shipping is employed, all the necessary packing is accomplished by simply wrapping the bottle of maggots in a layer of cellulose and inserting it into a carton for mailing. The postage on such a package is comparatively low, the weight being only about one-eighth that of iced packages. The excessive material and labor used in making up the iced package are also rendered unnecessary.

Nutritional retardation, therefore, seems applicable to various phases of maggot culture requiring the restrained growth and development of the maggots, and it makes the cultural process more simple, efficient and economical.

---

7. For some unknown reason the maggots in one bottle were dead on arrival at Ames, Iowa.

## SUMMARY

A retardation-inducing food, consisting of evaporated milk, agar and water, has been devised which eliminates the necessity for the customary method of retardation by low temperature, both during the sterility tests and during transit.

Tests were conducted to determine the rate of growth and development during nutritional retardation; it was found that both processes could be retarded for eight or nine days without serious injury. This possibility permits surgical maggots which are not needed immediately to be held for later use. It also enables long distance shipments to be made efficiently and with the minimum expense and labor.

A study has been made of the amount of necrotic tissue removed from the wound by maggots after various periods of nutritional retardation. This quantity is vastly greater than when retardation by low temperature is used. The therapeutic value of the maggots is thus greatly increased, as removal of necrotic tissue is apparently one of the principal factors in the value of this treatment. The amount removed varies inversely, however, with the length of the period of retardation, owing to the increased mortality. The period of feeding following retardation is from four to five days, and the maggots have a tendency to feed longer after an extended period of retardation than when growth has been arrested for only a short period.

Practical tests were conducted on shipments of nutritionally retarded maggots for long distances. Specimens mailed to various parts of the United States were reported as received in good condition and as feeding for four or five days after being transferred to necrotic tissue.



# PERITONEAL DRAINAGE

## RESISTANCE OF SINUS TRACT TO INFECTION

PHILIP SHAMBAUGH, M.D.

AND

ROBERT BOGGS, M.D.

BOSTON

Drainage of the peritoneal cavity has been shown to be a futile and, in fact, a harmful procedure in many of the conditions in which it was formerly advocated. There remain, however, three definite indications for the use of drains in the abdominal cavity: first, to control bleeding by the hemostatic effect of a foreign body; second, to provide an outlet for a localized infection of the peritoneal surface and thus to prevent formation of abscesses, and third, to produce a sinus tract through which substances may escape from a walled-off area within the abdomen without soiling the general peritoneal surfaces. In the third instance it is of considerable importance to know how soon the sinus tract forms and how soon the tissues comprising its walls become impervious to the passage of pathogenic organisms.

A number of investigators have shown that a foreign body left as a drain in the abdomen is shortly encapsulated by adherence of the surrounding peritoneal surfaces, so that the drain no longer communicates with the general peritoneal cavity. In 1905 Yates<sup>1</sup> made an admirable study of this problem in the dog. He observed that either gauze or rubber protective was entirely encapsulated within six hours and that the adhesions had become organized to form a structural tract at the end of three days. It is a familiar clinical observation that the abdominal sinus which remains after the removal of the drain a week or ten days postoperatively is just as resistant to infection as any other granulating wound. The number of days, however, that the drain must remain before the sinus tract can safely be exposed to pathogenic organisms has not been determined. The following experiments were undertaken to elucidate this point.

### METHOD OF INVESTIGATION

A virulent strain of *Bacillus coli*, secured from the department of pathology of the Peter Bent Brigham Hospital, was passed through a number of guinea-pigs until it had attained sufficient virulence to kill the pig within twenty-four hours after the intraperitoneal injection of 1 cc. of a twenty-four hour culture (approx-

---

From the laboratory of Surgical Research, Harvard Medical School.

1. Yates, J. L.: An Experimental Study of the Local Effects of Peritoneal Drainage, *Surg., Gynec. & Obst.* 1:473, 1905.

mately 500,000,000 organisms per cubic centimeter). A description of the experimental procedure follows.

The abdomen was shaved and cleansed with ether and 70 per cent alcohol. A small incision was made in the midline through the skin, muscle and peritoneum, and the layers of the abdominal wall on either side were approximated by silk sutures. A tube of gum rubber, 8 mm. in diameter, was inserted 3 cm. into the abdominal cavity, and a sterile dressing was held in place over the tube by an adhesive binder. At varying intervals after operation the tube was removed, the character of the sinus tract was noted and 1 cc. of the twenty-four hour culture of *B. coli* was introduced into the tract. The dressing was then reapplied. If the animal subsequently died, cultures were made of material obtained from the peritoneum through an incision made under aseptic precautions some distance from the sinus. If the animal was still alive after four days, it was killed, and similar cultures were made.

Similar experiments were carried out in a limited number of dogs. The culture used in these experiments was obtained from an animal dying of peritonitis induced by making a gaping incision in the lower part of the colon. Studies used as controls showed that, whereas as much as 50 cc. of this culture injected intraperitoneally was required to kill a dog, the peritoneal cultures remained positive as long as six days after the injection of 10 cc.

#### RESULTS

The nature of the sinus tract was observed at the following stages: At the end of twenty-four hours, removal of the tube left no visible tract. The intestine closed in and tended to bulge out of the wound on straining. In forty-eight hours a poorly formed tract was apparent, though the intestine still tended to protrude on straining. After three days a definite sinus tract had formed which did not collapse on removal of the tube.

In the first series, consisting of eight animals, the tube was removed on the first, second, third and fourth days after insertion, and a tight dressing was applied. All the animals survived, and the culture material obtained from the peritoneum four days after removal of the tube was negative in each instance.

In the second series, consisting of ten animals, the tube was removed after twenty-four hours, and 1 cc. of the culture was injected into the wound. Four pigs died and six survived until the fourth day. The cultures of peritoneal material obtained from three of these animals were positive, and those from three were negative.

In the third series the tube was removed after forty-eight hours, and an injection of the culture was made into the wound. One of the ten pigs died, and nine survived till the fourth day. The cultures of peritoneal material obtained from two of the nine pigs were positive, and those from seven were negative.

In the fourth series, the tube was removed after three days and an injection of the culture was made into the sinus. All ten pigs survived

till the fourth day, when cultures of peritoneal material yielded one positive and nine negative results.

In the fifth series, the tube was removed after four days and an injection of the culture was made into the sinus. All ten pigs survived, and the cultures of peritoneal material obtained on the fourth day were all negative.

In the sixth series, the tube was removed after five days and a portion of the culture was injected into the sinus. All five pigs survived, and the cultures of peritoneal material on the fourth day were all negative.

In the seventh series four dogs were used. The tube was removed, and 10 cc. of culture was injected into the tract on the second, third, fourth and fifth days, respectively. Cultures of material from the peritoneum obtained two days later were negative except in the case of the first dog.

#### COMMENT

It is seen that the resistance of the sinus tract rapidly increased, becoming complete by the fourth day. There was considerable resistance on the second day, in spite of the fact that the tract was so poorly formed that in most instances it was disrupted by removal of the tube. This may have been due to an increased local peritoneal resistance, resulting from the irritation of the foreign body.

It is interesting to compare the resistance of the peritoneal sinus to infection with that of healing sutured wounds of the skin and abdominal wall. The resistance of the latter type was worked out by DuMortier<sup>2</sup> in guinea-pigs, using a virulent strain of *Staphylococcus haemolyticus*. He determined that there was a rapid increase in resistance, so that by the fifth day it was comparable to that of intact skin. On the third day implantation of cultures of staphylococcus on the surface caused infection in 36 per cent of the animals, and on the fourth day in 10 per cent. Our results showed a slightly more rapid acquisition of resistance in the case of the peritoneal sinus. However, the fact must be considered that it takes, as a rule, a much larger number of organisms to infect the peritoneum than it does to cause an infection in the abdominal wall; hence a few organisms may have made their way through the wall of the sinus into the peritoneal cavity but were destroyed there by the time the animal was killed and a culture obtained.

From the foregoing observations it may be concluded that an abdominal drain of smooth rubber or rubber tissue may be safely removed after the third day without danger of infecting the general peritoneal cavity either by infection from without or by the evacuation

---

2. DuMortier, J. J.: The Resistance of Healing Wounds to Infection, *Surg., Gynec. & Obst.* 56:762, 1933.

of infected material along the sinus tract from within. This would probably not hold true in the case of drains in which there is exposed gauze, for with this type early removal disrupts the sinus tract. However even in this case, local peritoneal immunity would probably tend to prevent the spread of infection.

Certain clinical deductions may be drawn from the experimental study of the reaction of the peritoneal surfaces to drains. When the drain is inserted in a clean case to control bleeding, it should be removed prior to the third day or before a structural tract has formed, and this removal should be performed under strictly aseptic precautions. If the drain is allowed to remain longer than the third day, the resulting sinus tract may become infected, and, though there is little danger of infecting the general peritoneal cavity, convalescence is unnecessarily prolonged. When the drain is inserted to produce a sinus tract through which an underlying abscess may later be evacuated extraperitoneally, the drain may be removed as early as the third day, but preferably on the fourth or fifth day, and the abscess may be ruptured through the resulting sinus tract. The tract must, of course, be kept open by the reinsertion of a suitable piece of rubber tissue or tubing until the abscess has healed in. When the drain is inserted in infected peritoneal surfaces in which one suspects that an abscess would form if drainage were omitted, the drain should not be removed before the fourth day or before a structural tract is formed, and the tract must, of course, be kept open until it heals in from the bottom.

Furthermore, certain conclusions may be drawn as to the type of drain which should be employed. Exposed gauze should be avoided whenever possible. When the drain is for the control of bleeding and the hemostatic effect of the gauze is required, the "cigaret" type of drain should be employed and care be taken that only the gauze which is in direct contact with the bleeding tissue is left uncovered by the rubber casing. When the drain is inserted to provide an extraperitoneal outlet for infected material, a simple rubber tube is preferable. This tube should be smooth and soft but sufficiently rigid to produce a tract of suitable diameter to allow for subsequent irrigations.

Except for the control of bleeding, there seems to be little value in the incorporation of gauze in abdominal drains. For a few hours the gauze conveys serous exudate to the surface, but after that period it serves only as a plug to dam back purulent material which would find its way out through a simple rubber tube.

# PENETRATION OF MOIST HEAT APPLIED TO THE ABDOMEN AND ITS EFFECT ON INTESTINAL MOVEMENTS

HJALMAR E. CARLSON, M.D.

AND

THOMAS G. ORR, M.D.

KANSAS CITY, KAN.

The use of heat in the treatment of abdominal conditions, particularly peritonitis or localized abscesses, has become a frequent procedure in hospitals. Patients as a rule state that they feel better when such treatment is instituted, and the relief from pain which heat affords in intestinal or pelvic conditions is commonly known.

Some conflict of opinion is evident in the literature concerning the effect of heat applied locally to the abdomen. Among those who have found a rise in temperature within the abdomen after the application of heat to the outside of the abdomen are von Ewald,<sup>1</sup> von Brieger,<sup>1</sup> Wendriner,<sup>1</sup> Winternitz,<sup>2</sup> and Eichler and Schemel.<sup>3</sup> These authors used hot steam or jets of hot water to induce the increase in temperature. Chelmonski,<sup>1</sup> using hot water bottles, induced a rise of 2 C. within the abdomen, while Stengel and Hopkins,<sup>4</sup> using the same method, found the results negligible. Hepburn and his associates,<sup>5</sup> using hot water bags, hot wet packs, electric pads, irradiation with infra-red rays and diathermy, were unable to increase intragastric temperature after applying heat for one hour or longer, except with diathermy, by which a rise of 1 F. was noted. No studies recording the effect of heat on intestinal movements have been found in the literature.

---

From the University of Kansas School of Medicine.

1. Quoted by Eichler and Schemel.<sup>3</sup>

2. Winternitz, W., et al., in Cohen, S. S.: *System of Physiologic Therapeutics*, Philadelphia, P. Blakiston's Son & Company, 1902, vol. 9, p. 248.

3. Eichler and Schemel: *Ueber die Beeinflussung der Magentemperatur durch verschiedene hydrotherapeutische Applikationen und ihre Messung mit dem Fieberregistrierapparat*, *Deutsche med. Wchnschr.* **37**:2371, 1911.

4. Stengel, A., and Hopkins, A. H.: *A New Method for Determining the Intragastric Temperature in Man with Some Observations on Its Variations After Ingestion of Hot and Cold Liquids and During Digestion*, *Am. J. M. Sc.* **153**: 101, 1917.

5. Hepburn, J. S.; Eberhard, H. M.; Ricketts, A., and Rieger, C. L. W.: *Temperature of the Gastro-Intestinal Tract: The Effect Thereon of Hot and Cold Foods and of Physical Therapeutic Agents*, *Arch. Int. Med.* **52**:603 (Oct.) 1933.

## EXPERIMENTS

Heat was applied to the abdomen by using two thicknesses of moist flannel beneath an insulated rubber electric pad. The heating system was covered with a layer of rubber sheeting to prevent the loss of heat. The heat was usually applied for one hour and in some experiments for three hours. The temperature of the pack ranged between 106 and 109 F. at its point of contact with the skin.

The first ten determinations were made on two mature dogs weighing 10 Kg. each by taking the temperature with a long thermometer through the anus in the midcolon and in Thiry-Vella jejunal loops with the same mercury thermometer before and after heat had been applied for one hour. The abdomen of each animal was shaved, and the dogs were allowed to be in the room in which the experiments were carried out for at least an hour. The animals had had no food for at least twelve hours before the experiment was begun. The body temperature was taken through a slit in the axillary fold.

Fifteen determinations were made on three adult patients by taking the temperature in colostomy openings before and after the application of heat for one hour. The oral temperature was also recorded. Five observations were similarly made on a 9 year old child weighing 25 Kg. to determine the difference in effect produced by the thickness of the abdominal wall. These determinations were compared with five determinations made on a dog which weighed 25 Kg. Five observations were made on an adult having an infected suprapubic cystostomy wound to determine any difference in the conduction of heat between infected and non-infected areas. In each of the five patients studied the effect of heat applied for three hours was also observed.

The effect of heat on intestinal contractions was studied in the dog by applying heat to the abdomen and recording intestinal contractions on a smoked drum by means of a jejunal Thiry-Vella loop and a Brodie bellows. Heat was also applied by injecting warm water directly into the Thiry-Vella loop.

## RESULTS

The application of heat to the abdomen of small dogs for a period of one hour resulted in an average rise in temperature within the intestine of 1.2 F. (table). In one experiment no increase was noted and in another a drop of 0.6 F. occurred. The average rise in body temperature for the ten animals was 0.5 F. The largest dog showed an average increase of 0.9 F. in the intestine and a rise in body temperature of 0.3 F.

The experiments on adult patients with colostomies showed only a slight tendency to an increase of the temperature in the intestine. In eight of the experiments there was either no change or a drop in the temperature within the intestine. A small average rise of 0.2 F. was noted, with an average rise of body temperature of 0.1 F. The results on the child, however, were more definite: An average rise of 0.8 F. was noted.

The presence of infection did not seem to have any influence in either increasing or decreasing the penetration of heat. The average rise within the suprapubic cystostomy wound was 0.3 F.

The application of heat for a period of three hours did not significantly increase the intra-abdominal temperature in adults. In one patient the temperature remained unchanged after three hours. The child showed, however, a definite rise after a three hour period.

Kymographic tracings of the jejunum of the dog with the same heat applied to the abdomen as in the other experiments or with the appli-

*Comparison of Changes in Temperature (F.) After Moist Heat Had Been Applied to the Abdomen for One Hour to Show the Difference in Penetration Through Thick and Thin Abdominal Walls*

Temperature			Experiment					Average Rise in Temperature
			1	2	3	4	5	
Dogs; weight, 10 Kg.	1	Abdominal Before	102.0	103.6	104.0	102.2	103.6	Abdominal, 1.2
		After	103.2	106.2	105.4	103.6	104.6	
		Axillary Before	100.5	102.2	103.8	100.5	102.6	
		After	100.8	102.6	104.2	101.8	101.8	
	2	Abdominal Before	104.0	101.2	102.1	102.2	101.5	Body, 0.5
		After	105.5	103.0	102.1	101.6	103.4	
		Axillary Before	103.6	100.3	100.0	99.4	101.1	
		After	104.1	101.1	99.8	99.6	102.1	
Adults; weight, 60 Kg.	1	Abdominal Before	100.1	100.2	100.1	99.4	99.4	Abdominal, 0.3
		After	100.2	100.1	100.1	99.7	99.8	
		Oral Before	99.4	99.6	99.6	98.7	98.6	
		After	99.7	99.6	99.3	98.7	98.6	
	2	Abdominal Before	99.9	99.3	100.2	99.4	100.0	
		After	99.9	100.0	99.7	99.9	98.8	
		Oral Before	99.2	98.8	99.0	98.9	98.0	
		After	99.3	99.1	98.9	99.0	98.9	
	3	Abdominal Before	100.0	99.2	99.5	99.9	99.3	Body, 0.1
		After	100.0	99.6	99.4	99.9	99.4	
		Oral Before	98.6	98.6	99.1	98.7	98.9	
		After	98.5	98.7	99.4	98.6	98.8	
Child; weight, 25 Kg.	1	Abdominal Before	99.5	99.1	99.5	99.1	99.8	Abdominal, 0.3
		After	100.0	99.6	100.8	101.2	99.4	
		Oral Before	99.2	99.3	99.1	99.4	99.2	Body, -0.4
		After	99.0	99.0	98.9	98.8	98.4	
Dog; weight, 25 Kg.	1	Abdominal Before	101.0	102.5	101.1	101.5	101.4	Abdominal, 0.9
		After	101.6	103.8	102.0	102.0	102.5	
		Oral Before	99.5	101.1	99.5	100.0	101.1	Body, 0.3
		After	99.8	101.5	100.1	100.1	101.5	

cation of warm water directly into the intestine at the same temperature showed no tendency to an increase or decrease of either intestinal tone or amplitude of contractions.

#### SUMMARY

Warm moist heat was applied to the abdomen of small and large dogs, adults and a child for periods of from one to three hours in a total of forty experiments, and the temperature was recorded either in the colon or in an intestinal fistula. The effect of heat on intestinal

contractions was noted in dogs with Thiry-Vella loops by the use of kymographic tracings.

It was determined that local applications of heat to the abdomen produce a rise in temperature within the abdomen if the abdominal wall is not too thick. Definite penetration was noted in the child and in the dogs, but the penetration in the adults was negligible. Prolonged application of heat did not increase the degree of penetration.

The application of heat to the abdomen or of warm water to the intestine did not affect intestinal tone or intestinal movements.



# SUCTION WITH A NASAL CATHETER: ITS EFFECT ON THE BLOOD CHEMISTRY

REPORT OF A CASE

RICHARD F. NORTHROP, M.D.

PHILADELPHIA

Although articles in the literature dealing with continuous drainage of the intestinal tract through suction applied to an inlying nasal catheter are accumulating rapidly, there are at present very few. Although the duodenal tube was a prominent part of the surgeon's armamentarium and a device known as the Connell suction apparatus had been assembled, these aids were not united in therapeutic use until Ward,<sup>1</sup> in 1925, employed them in the treatment of "general peritonitis, postoperative ileus, intestinal obstruction and acute gastric dilatation" to prevent "that dilatation and soggyiness of the upper intestinal tract which is so commonly found in cases of this type that come to postmortem examination."

Following this rather brief suggestion there was silence until 1932, when Wangenstein,<sup>2</sup> in a treatise on acute intestinal obstruction, reported the successful treatment of three patients with obstruction by means of continuous suction applied through a nasal catheter. Interest in the subject has since been increasing rapidly, and the literature now includes several excellent articles by Wangenstein and Bartlett and the works of Paine, Carlson and Benjamin. These last three authors have concerned themselves chiefly with the application of suction in the treatment of postoperative nausea, vomiting and distention, while Wangenstein and Bartlett have more particularly studied its use in cases of ileus and of obstruction of the bowel.

Suction applied through a nasal catheter is recommended by Paine, Carlson and Wangenstein<sup>3</sup> for use as a routine following operation

---

From the service of Dr. H. L. Northrop, Hahnemann Hospital.

This thesis was submitted to the faculty of Surgery of the Graduate School of Medicine of the University of Pennsylvania in partial fulfillment of the requirements for the degree of Master of Medical Science (M.Sc. [Med.]) for graduate work in Surgery.

1. Ward, R.: An Apparatus for Continuous Gastric or Duodenal Lavage, *J. A. M. A.* **84**:114 (April 11) 1925.

2. Wangenstein, O. H.: Early Diagnosis of Acute Intestinal Obstruction with Comments on Pathology and Treatment, with Report of Successful Decompression of Three Cases of Mechanical Bowel Obstruction by Nasal Catheter Suction Siphonage, *West. J. Surg.* **40**:1 (Jan.) 1932.

3. Paine, J. R.; Carlson, H. A., and Wangenstein, O. H.: Postoperative Control of Distention, Nausea and Vomiting: Clinical Study with Reference to Employment of Narcotics, Cathartics, and Nasal Catheter Suction-Siphonage, *J. A. M. A.* **100**:1910 (June 17) 1933.

on the hiliary tract and gastric or intestinal operation, and Paine<sup>4</sup> recommended it in any case of postoperative distention with or without nausea and vomiting. Paine<sup>4</sup> further stated that patients who have undergone appendectomy or an operation for hernia probably have less nausea and vomiting and require fewer enemas when subjected to the intestinal decompression, but he expressed the belief that the advantages are too few to warrant its use, since it means retention of the tube in the nose for several days and a postponement of the return to fluids and food by mouth.

The indications for the use of suction by means of the nasal catheter in cases of obstruction of the bowels are clearly defined by Wangensteen and Paine<sup>5</sup> and include simple obstruction of the small intestine, spastic ileus and paralytic ileus. The authors are especially careful to insist that the chief contraindication is strangulation. Wangensteen<sup>6</sup> added: "Adhesive bowel obstruction is especially amenable to treatment by this method, whether the causative adhesive obstructing mechanism is of recent (postoperative) or remote origin."

While Wangensteen and Paine, with faith in the ileocecal valve, included among their contraindications cases in which an obstruction in the left colon caused dilatation of the proximal portion of the large bowel, Bartlett<sup>7</sup> disagreed, stating the belief that even here decompression may be effected, since at times the ileocecal valve is incompetent.

This paper was prepared in an effort to determine the effect of continuous duodenal drainage on the physiologic status of the organism and especially its effect on the quantity of chlorides in the blood and the carbon dioxide-combining power of the plasma. It was felt that dehydration could be studied by observing the changes in the concentration of the blood and in the urinary output. And, finally, an effort was made to determine an adequate means of combating the changes which might occur.

The apparatus used was in principle the same as that described by Wangensteen.<sup>2</sup> For some patients whose gastric contents were particularly thick and especially for patients with an emergency case who were not properly prepared it was found advantageous to use, instead of the routine no. 16 F Levine catheter, one of larger caliber, namely, no. 18 F. The larger catheter was tolerated just as well.

4. Paine, J. R.: Constant Suction by Nasal Catheter as an Adjunct in Post-operative Treatment, *Minnesota Med.* 15:444 (June) 1932.

5. Wangensteen, O. H., and Paine, J. R.: Treatment of Acute Intestinal Obstruction by Suction with Duodenal Tube, *J. A. M. A.* 101:1532 (Nov. 11) 1933.

6. Wangensteen, O. H.: Therapeutic Considerations in the Management of Acute Intestinal Obstruction, *Minnesota Med.* 15:556 (Aug.) 1932.

7. Bartlett, W., Jr., in discussion on Wangensteen and Paine.<sup>5</sup>

In the patients under observation, samples of blood were taken immediately before the operation. At the same time a specimen of urine was collected for examination. When the patient had reacted from the anesthetic sufficiently to swallow, the Levine catheter was passed through the nose and suction was instituted. At the same time, para-oral fluids, if any were to be used, were administered. No attempt was made to measure the amount of fluids taken by mouth nor the amount of fluids or gas recovered from the stomach. Morphine was given when necessary. To alleviate the irritation of the tube in the nose, 1 drop of 0.5 phenol in oil was dropped into each nostril every six hours, as suggested by Bartlett.<sup>8</sup> A 0.5 to 1 per cent solution made by dissolving several lozenges of ethylaminobenzoate in water was sprayed in the throat occasionally; it seemed to afford relief.

At the end of a twenty-four and a forty-eight hour period following the insertion of the nasal catheter, blood and urine were collected for study. The blood for the determination of the carbon dioxide-combining power was taken under oil and tested according to the method of Van Slyke. The blood chlorides were determined as outlined by Whitehorn. A modified Sahli technic was used in recording the hemoglobin.

In table 1 are outlined the results of duodenal drainage for forty-eight hours for thirteen patients, twelve of whom were operated on for a pathologic condition of the gallbladder or appendix. The thirteenth, Robert T., who was an ambulant patient with osteomyelitis, consented to drainage so that the list would include a near-normal person.

Under the column "Ketones in the Urine" are listed the values for acetone and diacetic acid as they appeared in the urine. The total amount of urine excreted in forty-eight hours is recorded, as is the amount of morphine required to control the pain. The maximum temperature and pulse readings are given. In this first group, no para-oral fluids were given. The patients drank water *ad libitum* so long as it returned immediately through the nasal tube.

In table 2 are recorded the results obtained in four cases in which fluids were given in the form of continuous venoclysis, either of saline solution and dextrose or of saline solution alone.

Table 3 shows the results in two cases in which the patients were given hypertonic (3 per cent) saline solution continuously by the intravenous route.

Table 4 shows the results when continuous hypodermoclysis was employed. In the last group (table 5) the material collected from the intestinal tract was placed in the rectum in the form of a 6 ounce (180 cc.) retention enema every four hours. The patients were limited to

---

8. Bartlett, W., Jr.: The Concept of Pyloric Balance in Ileus Treated by Continuous Suction from the Stomach, *Am. J. Surg.* 23:484 (March) 1934.

TABLE 1.—Results of Duodenal Drainage for Forty-Eight Hours in Patients to Whom No Para-Oral Fluids Were Given

Patient	Age	Operation	Time	Sodium Chloride of the Blood	Carbon Dioxide, Volume per Cent	Hemo- globin, Gm.	Red Blood Cells	Ketones in the Urine	Total Urine, Cc.	Morphine Sulphate Required, Grains	Temper- ature, F.	Pulse Rate
Robert T.	21	None	Preoperative	115	68.2	12.2	3,670,000		400	1/1	98.3	96
			24 hours after	379	70.2	13.9	4,550,000	+++				
William R.	40	Cholecystectomy	48 hours after	330	73.6	14.4	4,560,000		1,350	2/6	100.3	125
			Preoperative	379.5	68	15.3	4,910,000	.....				
			24 hours after	217	72.7	16.7	5,200,000					
			48 hours after	251	74.9	15.3	6,060,000					
Betty T.	21	Appendectomy	Preoperative	379	68.1	15.5	4,610,000	.....	1,650	3/6	100.2	116
			24 hours after	396	70.6	14.7	4,820,000	+++				
Rose D.	23	Appendectomy	48 hours after	379	79.6	16.2	4,770,000	+++		2/4	100	102
			Preoperative	396	55.1	13.7	4,100,000	+++	510			
Grace C.	28	Appendectomy	24 hours after	379.5	57	16	4,640,000	+++				
			48 hours after	379.5	70.2	13	5,280,000	+++	1,620	2/4	100	106
Nancy D.	10	Appendectomy	Preoperative	412	66.4	15.8	5,430,000					
			24 hours after	412	74	15.8	4,740,000	+++				
Mary D.	34	Appendectomy	48 hours after	346.5	77.7	17	5,390,000	+++	1,350	1/6	98.4	126
			Preoperative	412	61.5	14.9	4,170,000	+++				
Louise S.	17	Appendectomy	24 hours after	412	64.3	13.7	4,310,000	+++				
			48 hours after	379	70.2	16	5,020,000	+++	840	2/6	100.2	116
Jean M.	21	Appendectomy	Preoperative	429	58.9	12.2	5,010,000	No specimen				
			24 hours after	396	57	14.8	4,600,000	+++				
Elizabeth T.	30	Cholecystectomy	48 hours after	297	61.5	15.5	5,190,000	+++	1,650	1/6	99.2	92
			Preoperative	412	58.9	14.9	4,640,000	+++				
Laura L.	21	Appendectomy	24 hours after	363	66.4	17.2	5,230,000	+	1,140	2/6	100.2	116
			48 hours after	363	62.6	17.4	5,650,000	+				
Mary F.	16	Appendectomy	Preoperative	396	46.6	12.8	4,680,000	No specimen				
			24 hours after	379	61.5	15.7	4,430,000	+++	690	1/4	100	124
Betty D.	33	Appendectomy	48 hours after	297	61.5	17.2	4,690,000	+				
			Preoperative	379.5	68.3	17	4,800,000	No specimen				
Mary F.	16	Appendectomy	24 hours after	363	55.1	17.4	5,210,000	+++	1,650	1/6	100	92
			48 hours after	412.5	51.3	15.8	4,720,000	+++				
Betty D.	33	Appendectomy	Preoperative	495	61.5	15.8	4,340,000	No specimen				
			24 hours after	465	49.1	11.8	4,320,000	+++	750	2/6	99.2	120
Betty D.	33	Appendectomy	48 hours after	412.5	51.3	15.1	5,550,000	+++				
			Preoperative	462	41.4	17.4	5,160,000	+++				
Betty D.	33	Appendectomy	24 hours after	412.5	60.7	16	4,720,000	+				
			48 hours after	429	71	11.8	4,570,000	+++	810	1/1 and 1/6	101.4	116
Betty D.	33	Appendectomy	Preoperative	412.5	61.6	14.7	4,570,000	No specimen				
			24 hours after	396	55.1	16.7	4,430,000	+++				
Betty D.	33	Appendectomy	48 hours after	379.5	68.3	13.4	4,510,000	+++				

TABLE 2.—Results of Duodenal Drainage for Forty-Eight Hours in Patients Who Received Continuous Venoclysis

Patient	Age, Years	Operation	Total Amount of Fluid Given	Time	Sodium Chloride of the Blood	Carbon Dioxide, Volume per Cent	Hemo-globin, Gm.	Red Blood Cells	Ketones in Urine	Total Urine, Cc.	Morphine Sulphate Required, Grains	Temperature, F.	Pulse Rate
Anthony V.	36	Cholecystectomy	Saline solution with 5 per cent sugar, 3,000 cc.	Preoperative 24 hours after 48 hours after	363 445 462	68.3 53.2 68.3	14.9 14.4 13.7	5,010,000 4,650,000 3,920,000	.....	1,530	2/4	100.4	108
Freda H.	21	Ovarian cyst and appendectomy	Saline solution with 5 per cent sugar, 7,000 cc.	Preoperative 24 hours after 48 hours after	396 445 462	63.4 63.5 72.1	13.7 10.4 12	4,580,000 5,000,000 4,020,000	Sugar +	2,100	3/4	100.4	118
Helen C.	21	Appendectomy (perforated)	Saline solution, 3,800 cc., and sugar 100 Gm.	Preoperative 24 hours after 48 hours after	429 495 511	58.6 66.4 62.6	13 11.7 11.3	4,110,000 4,190,000 4,660,000	+++ +++ +++	1,920	3/6	102	120
Herbert W.	23	Appendectomy (perforated)	Saline solution, 4,000 cc.	Preoperative 24 hours after 48 hours after	412 330 313	81.5 85.7 74.9	16.9 16.2 14.3	5,060,000 5,000,000 4,650,000	.....	2,190	3/4	101	104

TABLE 3.—Results of Duodenal Drainage for Forty-Eight Hours in Patients Who Received Continuous Venoclysis with 3 Per Cent Saline Solution

Patient	Age, Years	Operation	Total Amount of Fluid Given	Time	Sodium Chloride of the Blood	Carbon Dioxide, Volume per Cent	Hemo-globin, Gm.	Red Blood Cells	Ketones in Urine	Total Urine, Cc.	Morphine Sulphate Required, Grains	Temperature, F.	Pulse Rate
Helen D.	18	Appendectomy	Sugar, 25 Gm., and 3 per cent saline solution, 2,600 cc.	Preoperative 24 hours after 48 hours after	495 485 379	60.5 58.9 62.6	12.8 12.2 9.2	4,780,000 4,270,000 3,360,000	++	2,190	2/6 and 1/4	101.4	112
Helen S.	52	Appendectomy	Sugar, 25 Gm., and 3 per cent saline solution, 2,900 cc.	Preoperative 24 hours after 48 hours after	445 412 330	70.2 57 47.5	16.7 14.1 12.2	5,270,000 4,920,000 3,820,000	+	2,190	2/6	102.4	128

TABLE 4.—Results of Duodenal Drainage for Forty-Eight Hours in Patients Who Received Continuous Hypodermoclysis

Patient	Age, Years	Operation	Total Amount of Fluid Given	Time	Sodium Chloride of the Blood	Carbon Dioxide, Volume per Cent	Hemo-globin, Gm.	Red Blood Cells	Ketones in Urine	Total Urine, Cc.	Morphine Sulphate Required, Grains	Temperature, F.	Pulse Rate
Mary L.	65	Cholecystectomy	Saline solution, 2,600 cc.	Preoperative 21 hours after 48 hours after	489 303 445	72.1 58.7 56	14.1 13.6 13.4	4,110,000 4,500,000 4,560,000	..... + .....	1,110	1/4	101.1	132
Mary G.	50	Cholecystectomy and appendectomy	1 per cent sugar solution, 3,000 cc., and saline solution, 5,200 cc.	Preoperative 21 hours after 48 hours after	306 412.5 429	62.1 51.1 60.9	12.8 12.2 13.9	4,580,000 5,010,000 4,510,000	.....	1,170	3/4	100.3	136
Regina K.	27	Appendectomy	Saline solution, 3,000 cc.	Preoperative 21 hours after 48 hours after	478.5 475.5 390	66.4 71.1 66.4	16.2 13 13.7	4,320,000 4,130,000 4,600,000	No specimen +++- ++-	930	1/6	100	100

TABLE 5.—Results of Duodenal Drainage for Forty-Eight Hours in Patients Whose Intestinal Drainage was Replaced in the Rectum

Patient	Age, Years	Operation	Total Amount of Fluid Given	Time	Sodium Chloride of the Blood	Carbon Dioxide, Volume per Cent	Hemo-globin, Gm.	Red Blood Cells	Ketones in Urine	Total Urine, Cc.	Morphine Sulphate Required, Grains	Temperature, F.	Pulse Rate
Mary F.	19	Appendectomy	Drainage material in rectum, 1,800 cc.	Preoperative 21 hours after 48 hours after	336 412.5 379	60.7 55.1 70.2	14.2 13.6 13	4,730,000 4,810,000 4,300,000	No specimen ..... ++	1,710	2/6	100	129
Dolores H.	21	Appendectomy	Drainage material in rectum, 1,800 cc.	Preoperative 21 hours after 48 hours after	429 511.5 370.5	58.9 60.4 70.2	16.5 12.2 13.9	4,430,000 4,240,000 5,350,000	+ ++ ++	720	0	99.3	102
Gertrude D.	40	Appendectomy	Drainage material in rectum, 1,800 cc.	Preoperative 21 hours after 48 hours after	415 330 330	60.7 64.6 60.0	13.9 13.9 14.8	4,710,000 4,520,000 4,570,000	++- ++ ++	1,620	0	98.4	116

8 ounces (240 cc.) of water an hour by mouth, so that the material aspirated would not be diluted too much. The intestinal contents were collected in a bottle inserted in the circuit, and the amount required was withdrawn when necessary, strained, heated and given as an enema.

In an analysis of the results shown in table 1 it is seen that the patients almost uniformly suffered a drop in blood chlorides and an elevation of the carbon dioxide-combining power. The blood became concentrated, as evidenced by the rise in the hemoglobin content and in the number of red cells. Ketones appeared in the urine, in spite of the alkalosis. In their book on biochemistry Trumper and Cantarow<sup>9</sup> explained this as being due (in obstruction of the pylorus and the upper part of the intestinal tract associated with continued vomiting) possibly to starvation and privation of carbohydrates, but, they added: ". . . in all forms of alkalosis it is probable that the diminution in hydrogen-ion concentration diminishes carbohydrate utilization in the tissues and thus interferes with the normal combustion of fatty acids in a manner similar to that operating in diabetes mellitus."

The total amount of urine voided by these patients daily was in only four cases more than the 700 cc. that Bartlett<sup>8</sup> mentioned as the upper border of dehydration.

As dehydration advanced and the patients leaned toward alkalosis, the majority showed flushed faces and marked thirst; otherwise the changes produced no symptoms. All the patients were comfortable abdominally, showing no distention, nausea or vomiting. Carlson and Orr,<sup>10</sup> in an article describing an experiment in which high intestinal obstruction was produced in dogs, reported the changes in the blood in the animals which were fed water and in those which were not and concluded that, in spite of the changes in the blood, which are more marked in the former group, "continuous lavage of the stomach in acute intestinal obstruction is a beneficial part of the treatment."

The four patients data for whom are given in table 2 were in a more serious condition than the others and were subjected to continuous venoclysis. As may be seen, although the carbon dioxide-combining power still showed a rise toward alkalosis, the administration of saline solution had caused a rise in the chloride content of the blood and had eliminated the dehydration. Herbert W., in a state of definite alkalosis on admission, showed this condition corrected under the administration of saline solution.

---

9. Trumper, M., and Cantarow, A.: *Biochemistry in Internal Medicine*, Philadelphia, W. B. Saunders Company, 1932, p. 203.

10. Carlson, H. E., and Orr, T. G.: *Experimental Obstruction of Jejunum: Effect of Administration of Water on Length of Life and Changes in Chemical Composition of Blood*, Arch. Surg. 28:292 (Feb.) 1934.

Even the administration of a 3 per cent saline solution did not check the drop in the blood chlorides in the two patients data for whom are shown in table 3. The intake of fluid apparently was adequate, since there was no evidence of dehydration. The thirst evidenced by these patients was even more marked than that evidenced by the others.

Continuous hypodermoclysis to some extent controlled the changes in the blood, as shown in table 4, and the changes in the red blood cell count and in the hemoglobin were not so marked as those shown in table 1, but the urinary output was diminished. Mary L. at the end of forty-eight hours of drainage started to have severe fibrillation and for twenty-four hours required infusions of 10 per cent dextrose solution and digitalis by mouth. The heart assumed normal rhythm again, however, in thirty-six hours. The mishap perhaps was due to an alteration in the volume of blood.

Finally, as suggested by Roberts,<sup>11</sup> the drainage material was introduced into the rectum every four hours (table 5). No rectal irritation was caused, and litmus paper showed that the specimens were either acid or neutral. The dehydration in two of the three cases was apparently controlled, and there was an initial rise in the amount of blood chlorides in two, but between the twenty-four and the forty-eight hour period specimens the chloride content fell. Possibly this was due to dilution of the material by water, which was drunk at the rate of 8 ounces an hour. These three patients appeared more comfortable than any of the others, and two required no sedative during their postoperative course.

The following is the report of a case of obstruction of the bowel of the adhesive type in a patient who recovered under therapy with suction:

#### REPORT OF A CASE

Ralph N., a Negro boy aged 12, was admitted to the hospital on Jan. 28, 1934, and a provisional diagnosis of acute appendicitis was made. He had an abdominal scar on the right side near the umbilicus which was said to be the result of an operation for the removal of a safety pin which he had swallowed when an infant. He was operated on immediately, and an acutely inflamed appendix was removed. The small intestine was rather markedly distended and was firmly adherent to the abdominal wall at the site of the former operation. These adhesions were freed, but during the procedure large areas of visceral peritoneum were torn from the bowel. The child's condition did not permit adequate exploration.

Twenty hours following operation the child vomited and the abdomen became distended. In spite of fair results from enemas, the vomiting and distention increased until fifty-one hours following operation, on January 30, a duodenal

11. Roberts, C. G.: Transduodenal Decompression and Reintroduction by Proctoclysis of Gastro-Intestinal Drainage in Acute Mechanical Ileus, *J. A. M. A.* 102:1149 (April 7) 1934.



catheter was inserted through the nose and suction was applied. The vomiting ceased at once, and in three hours the abdomen was flaccid. Fluids were given by hypodermoclysis, and the child remained comfortable until February 1, when the tube was withdrawn because of a normal pyloric reflex.<sup>12</sup> For the next few days the distention was partially controlled by enemas; a soft diet was attempted, but after the first meal caused vomiting the child refused another and was again given only liquids. On February 6, the distention became so marked and vomiting was so persistent that the tube was again inserted and continuous venoclysis of 5 per cent dextrose in saline solution was begun. At this point the enemas were entirely ineffective; the distended coils of intestine were clearly visible through the abdominal wall, and peristalsis was apparent to the eye. The patient was comfortable from this time on. The tube was removed again on February 8, and a high compound enema was effective. A liquid diet was begun, and the venoclysis stopped, 4,000 cc. having been given in the two and a half days it was employed. The intestinal tract was kept open with liquid petrolatum. No further nausea, vomiting or distention occurred, and the patient was discharged in good health on February 22.

#### SUMMARY

The effect of continuous drainage of the stomach and duodenum through a nasal catheter was studied in twenty-five patients, twenty-four of whom were operated on.

Continuous suction applied through a nasal catheter causes a drop in the blood chlorides, an elevation of the carbon dioxide-combining power toward or into alkalosis, an elevation of the hemoglobin content of the blood and an increase in the red blood cell count.

The marked changes in the chlorides, hemoglobin and red cell content of the blood and the changed carbon dioxide-combining power accompanying continuous lavage of the upper intestinal tract produce few, if any, untoward symptoms.

Of the various methods of administering para-oral fluids, continuous venoclysis appears to be most effective in controlling the changes in the blood incident to continuous duodenal suction.

Administration of the aspirated intestinal contents in the form of retention enemas does not cause rectal irritation and deserves further study as a means of combating postoperative dehydration and the loss in chlorides and the alkalosis incident to obstruction of the bowels and continuous lavage of the stomach.

The use of a properly functioning nasal catheter with applied suction is an efficient way of controlling postoperative nausea, vomiting and distention and should be used prophylactically in cases in which this triad is anticipated.

A case of obstruction of the bowel of the adhesive type, of recent (or remote?) origin is reported, and the use of duodenal suction in the case is described.

---

12. Bartlett, W., Jr.: *The Changing Attitude Toward Ileus*, Surg., Gynec. & Obst. **57**:702 (Nov.) 1933.

# ACUTE PANCREATITIS

FRANCIS F. HENDERSON, M.D.

AND

E. S. A. KING, M.D.

BOSTON

Acute pancreatitis is an emergency condition that has interested the surgeon for many years. In spite of a large amount of study the results of treatment have not shown improvement in any degree comparable to that obtained in the case of many other abdominal diseases. From a study of the literature it is seen that the mortality rate varies between 40 and 80 per cent. During the last fifteen years, sixty patients with proved cases have been operated on at the Boston City Hospital. No report of an appreciably larger series has ever been published. This paper is based on a study of the literature and of these sixty cases.

## ETIOLOGY

The hypotheses as to the etiology of acute pancreatitis presented by different students of the disease vary considerably. There has been a stereotyped classification of the etiology which practically every author recognizes, but there is no clearcut idea as to the importance of the different factors.

Pancreatic infection by the lymphatic route based on the anastomosis and relation of the lymphatics between the gallbladder and the pancreas (chiefly the head) has been given much consideration.

Pancreatic infection through the bile ducts has been considered important, and much reference has been made to it, proving that the injection of sterile bile, infected bile and the various bile salts into the pancreatic ducts results in acute pancreatic necrosis simulating the pathologic picture which is frequently seen at operation. Again, the etiology has been considered from the standpoint of duodenal contents being forced into or aspirated into the pancreatic ducts. Retrojection of bile due to spasm of the sphincter of Oddi is the hypothesis of Archibald. Again, the lodging of a gallstone in the ampulla of Vater, above which the bile duct and the duct of Wirsung have a common opening, has been discussed and found to be the cause in about 4.5 per cent of the cases.

Pancreatic infection by way of the blood stream is a possibility; it has developed in the course of some infectious diseases such as typhoid, influenza, furunculosis and parotitis. It is a well known fact that,

---

From the Fifth Surgical (Harvard) Service of the Boston City Hospital.

especially in children, there is an involvement of the pancreas simulating acute pancreatitis that develops during the course of mumps.

Pancreatic infection by direct contiguity has also been discussed. Such conditions as perforation of a gastric or duodenal ulcer or carcinoma of the stomach with ulceration may cause pancreatic infection in a few cases. However, in going over the literature it is noted that within the last ten years only three cases have been reported in which a perforated ulcer was associated with acute pancreatitis. In a series of thirty autopsies performed at the Boston City Hospital in cases of acute pancreatitis, accompanying perforated gastric ulcer has been present in only one instance. The coexistence of disease of the gallbladder with acute pancreatitis has been prevalent in the experience of most authors, and especially in the German literature disease of the gallbladder and bile ducts holds the highest place by far among the associated etiologic factors. The marked difference between the pathology and pathogenesis of pancreatitis and those of all other acute infections is due to the fact that once the pancreatic tissue is sufficiently involved to result in activation of the trypsinogen the resulting trypsin proceeds to digest the organ itself and often neighboring tissues. This activation of trypsinogen may occur as a result of damage brought about by any of the aforementioned etiologic factors.

#### INCIDENCE

*Age.*—Table 1 demonstrates the incidence of acute pancreatitis according to age and points out that the highest incidence is between 30 and 60 years.

TABLE 1.—*Age by Decades*

Years	Cases
18 to 20.....	2
20 to 30.....	5
30 to 40.....	16
40 to 50.....	15
50 to 60.....	16
60 to 70.....	6
Total cases .....	60

The youngest patient in this series was 18 years of age, and the oldest, 70. The average age for males was 45.3 years and for females, 42.5 years. The average age for both sexes was 43.9 years.

*Sex.*—There is a preponderance of acute pancreatitis in the female sex, which is borne out in all tabulated series of cases of this disease. In this series there were thirty-five females and twenty-five males. The increased incidence of this disease in women is probably influenced somewhat by the frequency with which disease of the gallbladder occurs in this sex.

*Color.*—Of the sixty patients, four were colored, and all of these were of the female sex.

## PHYSIOLOGY AND PHYSIOLOGIC CHEMISTRY

In experimentally produced pancreatitis in dogs there is an increase in the urea nitrogen and in the nonprotein nitrogen content of the blood in about two thirds of the cases. There is no change in the amount of chlorides. A slight increase in the carbon dioxide-combining power is found in a few cases. The change in nitrogenous elements closely simulates that in cases of experimental peritonitis, acute intestinal obstruction and dehydration. In all cases of pancreatic deficiency the following changes occur: Toxins form as a result of incomplete digestion of protein. There is an increase in bacterial activity in the intestines, which causes fermentation with the partly converted sugars. There is irritation of the intestines from the incompletely split fatty acids. In acute pancreatitis there is an increase in unsplit fat in the stools as well as an increased output of nitrogen in the urine not related to the intake of food. Glycosuria and an elevated blood sugar are sometimes found, but they are by no means constant.

There is an increase in diastase in the urine owing to the liberation of pancreatic ferments. The normal diastase in the urine varies from 8 to 32 units. In well defined cases of pancreatitis it is usually well over 100. In a recent case, not included in this series, there was a pre-operative diastase reading of 128 and twenty-four hours following operation the value increased to 1,024 plus. Some types of disease of the gallbladder, peritonitis and severe glycosuria will increase the diastase content of the urine. This must be considered in interpreting this test. It is of interest to note that in a recent case of a ruptured infarct of the right lobe of the liver with profuse hemorrhage into the peritoneal cavity, producing a picture which closely resembled acute pancreatitis, the diastase reading was 128.

## SIGNS AND SYMPTOMS

The signs and symptoms described are those which this series of patients presented on admission to the hospital and during their course of observation.

*Pain.*—The pain chiefly described has been that occurring in the epigastrium, at first steady and then intermittent, occurring in a rather rhythmic fashion. This pain has been described as being at its height sharp, stabbing and knifelike. The initial pain lasted from one to two hours, with relief for several hours, followed by an exacerbation of the same description. In most of the cases the pain did not radiate. In four cases it radiated to the tops of both shoulders. In two cases it radiated to the umbilicus; in two cases it radiated to both costal margins. In two cases it was referred to the small of the back. In no case did the pain radiate to the angle of the left scapula as is sometimes described. Pain was not relieved by morphine to the same extent that biliary colic

and renal colic are relieved, a classic feature of this disease. The onset of the pain in every case was sudden. In twenty-three cases there were recurrent attacks of epigastric pain dating anywhere from two weeks to fifteen years prior to the onset of the last attack. The previous attacks were all less severe than the one which brought the patient to the hospital.

*Nausea and Vomiting.*—In all cases there were associated nausea and vomiting following the pain. The first vomiting was continuous, with apparent evacuation of the contents of the stomach, following which there was retching at intervals; the patients described a regurgitation of bitter greenish material. In one case vomiting of frank blood was present.

*Other Symptoms.*—About 30 per cent of the patients gave a history of constipation. In no case was diarrhea present. Shortly after the onset of pain most of these patients described oncoming or gradually increasing distention of the abdomen with little relief obtained by enemas, a feature which makes one consider the possibility of intestinal obstruction.

All of these patients were either extremely well nourished or obese. On admission the patients were prostrated, five showing cyanosis and eight a slight icteric tint. On admission to the hospital the picture of shock was not present, and any shock which may have been associated, as is often described, must have been present at the onset. The pulse varied from 100 to 120 in rate and was of fair quality. The temperature varied between extremes of 96 F. in four cases and 103.5 in three, the remainder being between 98.6 and 101 F.; the average temperature was 99.2 F. The respiratory rate varied between 20 and 24. Examination of the head and neck revealed no significant signs. There were no associated findings in the chest or heart definitely related to acute pancreatitis, although moist râles were frequently present at the bases of both lungs at the time of admission. This can be explained by the close relationship of the pancreas to the diaphragm. Interference with diaphragmatic excursion results in a decrease in the expansion of the lungs and therefore hypostasis of the bases.

*Signs.*—The abdominal findings were the most significant symptoms at physical examination. Abdominal breathing was limited in practically all the cases and absent in many. Palpation revealed a characteristic soft distention below the umbilicus with an increasing mild spasm and rigidity above the umbilicus, but this was not by any means boardlike. The tenderness in the upper half of the abdomen was constant, definite and most severe in the midepigastrium. The next most common place was the right upper quadrant. In only one case was a mass palpable in the epigastrium. In no case was there ecchymosis in either flank. In five

cases, shifting dulness was noted. In many cases there was a rather diffuse tenderness over the lower, softly distended, portion of the abdomen, but it was not marked to any degree in any one place. In practically all the cases peristalsis was present, and in some it was definitely increased.

#### LABORATORY FINDINGS

The average white blood cell count was 17,000. Red cell counts were not made for every patient, but none of those which were made fell below 4,500,000; the highest was 5,054,000.

Sixteen patients showed a slight but definite trace of albumin in the urine. Four patients showed glycosuria. Acetone and diacetic acid were present in one case. The urine in all other cases was essentially normal.

#### SUMMARY OF CHARACTERISTICS

The characteristics of acute pancreatitis may be summarized as follows: prostration of the patient; severe, rhythmic, intermittent epigastric pain; recurrent retching and vomiting; softness and distention of the lower part of the abdomen; epigastric tenderness with mild spasm of the upper part of the abdomen; occasional slight jaundice, and occasional cyanosis.

The laboratory findings are an increased amount of diastase in the urine, a high red cell count, an increased white cell count and a comparatively low temperature. Glycosuria may or may not be present.

#### DIFFERENTIAL DIAGNOSES

In the literature extensive lists of other conditions are frequently considered under the heading of differential diagnosis. In the present series, the following diagnoses were seriously considered in one or more cases: perforated gastric or duodenal ulcer, acute cholecystitis, intestinal obstruction, subdiaphragmatic abscess, acute appendicitis, renal calculus, peritonitis, lobar pneumonia, diaphragmatic pleurisy, perinephritic abscess, coronary disease, ruptured ectopic pregnancy, pleurodynia and infarct of the liver.

#### SURGICAL PATHOLOGY

At exploration, in twenty-nine of the cases in this series there was free fluid in the peritoneal cavity. In twenty-six instances the fluid varied from serosanguineous to dark brown, the latter type representing old blood free in the peritoneal cavity. In three cases the fluid was of a clear straw-colored type. In eight cases fluid was found in the lesser peritoneal sac. In each of these the fluid consisted of old blood, pus and necrotic tissue of the sac. Organization of this material sometimes encapsulated the entire pancreas. Fatty necrosis was a common finding,

being present in forty cases. It was distributed in the great omentum, the adjoining viscera and the mesentery, over the pancreas and through the lesser sac. It was characterized by small islands made up of numerous small white areas averaging from 2 to 3 mm. in diameter. These islands of fatty necrosis alternated with normal areas of fat. In thirty-eight cases a hard, indurated pancreas was noted; it had swollen to from two to three times its normal size and was a somewhat reddish brown. In some of these cases, however, there were punctate hemorrhages under the capsule. A soft, necrotic pancreas was found in sixteen cases, and in six cases the pancreas was normal in size and consistency except for small areas of fatty necrosis. The small as well as the large intestines showed moderate distention.

TABLE 2.—*Type of Operation Performed*

Type of Operation	Cases	Deaths	Mortality, per Cent
Cholecystostomy plus drainage of pancreas.....	29	14	48
Cholecystectomy plus drainage of pancreas.....	7	4	57
Drainage through foramen of Winslow.....	9	5	55
Drainage of pelvis.....			
Drainage of pancreas alone.....	15	9	60

TABLE 3.—*Length of Time from the Onset of Symptoms to Operation*

Interval Before Operation	Cases	Deaths	Mortality, per Cent
0 to 12 hours.....	17	12	64
12 to 24 hours.....	12	7	58
24 to 48 hours.....	15	6	40
2 to 6 days.....	9	2	22
7 to 12 days.....	4	2	50
12 days plus.....	3	3	100

Of the sixty patients, thirty-three (55 per cent), showed some type of associated disease of the gallbladder. Thirteen patients (21.7 per cent) showed a large, tense gallbladder. Fifteen (25 per cent) showed chronic cholecystitis plus stones, and five (8.3 per cent) showed macroscopically a pathologic picture of chronic cholecystitis without stones.

#### TREATMENT

In most clinics acute pancreatitis has been recognized as presenting a surgical emergency. Immediate operation has been advised by nearly all authors. The type of operation, however, varies in different clinics and in different cases in the same clinic. The indications vary with the different conditions found on exploration. In this series the operations performed are shown in table 2.

This table demonstrates that the lowest mortality rate occurred in cases in which the gallbladder and the pancreas were drained. The drainage of the pancreas in these cases was through the gastrohepatic omentum or the gastrocolic omentum. The drainage of the pancreas was induced by blunt dissection with the

finger so as to avoid extensive hemorrhage. Extensive splitting of the capsule and perforating pancreatic tissue leads to further liberation of pancreatic ferments and hemorrhage.

In table 3 the operations are classified according to the length of time from the onset of symptoms to the operation.

If all the cases were of equal severity this table would prove that the optimum time for operation is from two to six days after the onset. But possibly the patients who were operated on earlier had the more fulminating cases, and perhaps many of those who died would have died anyway. In spite of this, however, the difference in results between early and somewhat delayed operation indicates that delay should deliberately be tried in cases of all degrees of severity in a large series. There is little doubt that in a process as diffuse as this suggestive measures (nothing given by mouth, hypodermoclysis and administration of morphine) will probably allow nature to wall the process off to some extent and make the operation safer when it is performed.

Table 4 indicates the anesthetic used and the accompanying mortality.

TABLE 4.—*Mortality with Various Anesthetics*

Anesthetic	Cases	Deaths	Mortality, per Cent
Nitrous oxide, oxygen and ether.....	46	22	47
Spinal .....	10	6	60
Local .....	4	4	100

Anesthesia produced by nitrous oxide, oxygen and ether was accompanied by the lowest mortality rate. That ten operations were performed under spinal anesthesia is not sufficient proof of its value. The significance of local anesthesia cannot be evaluated from this series, because the four patients operated on were practically moribund from the beginning.

#### SUMMARY

The cases of sixty patients with acute pancreatitis treated surgically have been studied.

The incidence of disease of the gallbladder occurring with acute pancreatitis was 55 per cent.

The mortality rate was 53.3 per cent.

Cholecystostomy plus drainage of the pancreas through the gastro-hepatic or gastrocolic omentum was the safest operation.

Nitrous oxide, oxygen and ether anesthesia was accompanied by the lowest mortality.

The fact that the mortality rate was the lowest in patients operated on from the second to the sixth day is of considerable interest. We realize that this series of cases is too small to warrant definite conclusions, but the results lead one to think that acute pancreatitis does not present as much of a surgical emergency as has been previously thought.

It is our plan in the future to be conservative in the treatment of acute pancreatitis and to delay operation to some time between the



second and sixth day, choosing the time when the patient's condition appears to have reached a maximum degree of recovery from the initial toxemia.

## BIBLIOGRAPHY

- Archibald: Surg., Gynec. & Obst. **28**:529, 1919.
- Bernhard, F.: Relation Between Diseases of Biliary Passages and Appearance of Necrosis; Aids in Diagnosis of Pancreatic Disease, *Deutsche Ztschr. f. Chir.* **23**:1, 1931.
- Brody, W., and Custer, R. P.: Acute Hemorrhagic Necrosis of the Pancreas, *Am. J. M. Sc.* **184**:389 (Sept.) 1932.
- Cabot: Acute Hemorrhagic Pancreatitis, *New England J. Med.* **199**:536, 1928, case 14,302.
- Chamberlain, D.: Acute Pancreatitis, *Brit. J. Surg.* **14**:390, 1929.
- Classen, A. C.; Orr, T. G.; Johnstone, P. M., and Rice, B.: Chemical Changes in the Blood of Dogs in Experimental Pancreatitis, *J. Lab. & Clin. Med.* **13**:457 (Feb.) 1933.
- Covaro, A. A.: Acute Hemorrhagic Pancreatitis in Thirteen Year Old Girl, *Prensa méd. argent.* **18**:149, 1931.
- Cullen, T. S., and Friedenwald, J.: Acute and Chronic Pancreatitis; Clinical Observations, *Arch. Surg.* **15**:1 (July) 1927.
- Deaver, J. B., and Pfeiffer, D. B.: *Ann. Surg.* **58**:151, 1913.
- Delmore, J. L.: Acute Pancreatitis, *Minnesota Med.* **11**:80, 1928.
- de Takáts, Géza, and Mackenzie, W. D.: Acute Pancreatic Necrosis and Its Sequelae, *Ann. Surg.* **96**:418 (Sept.) 1932.
- Dragstedt, L. R.; Haymond, H. E., and Ellis, J. C.: Pathogenesis of Acute Pancreatitis (Acute Pancreatic Necrosis), *Arch. Surg.* **28**:232 (Feb.) 1934.
- Eggers, C.: Acute Pancreatitis, *S. Clin. North America* **9**:743, 1929.
- Grant, J. W.: Acute Necrosis of the Pancreas, *Brit. M. J.* **1**:1101, 1928.
- Diagnosis and Treatment of Acute Pancreatitis, *Clin. J.* **58**:61, 1929.
- Hanson, A. M.: Application of Physiological Chemistry to Pancreatitis, *Mil. Surgeon* **70**:244 (March) 1932.
- Henle, C.: Acute Pancreatitis Developing After Resection of Stomach for Perforated Ulcer, *Arch. f. klin. Chir.* **161**:747, 1930.
- Hopkins, P. E.: Acute Pancreatitis, *Illinois M. J.* **60**:109, 1931.
- Horine, C. F.: Acute Pancreatitis, *Ann. Surg.* **99**:300 (Feb.) 1934.
- Kaufman: Surg., Gynec. & Obst. **1**:529, 1919.
- Kreiner, W.: Acute Pancreatitis with Hyperglycemia: Two Cases, *Zentralbl. f. Chir.* **55**:1219, 1928.
- Kummer: Hemorrhagic Pancreatitis: Eight Cases, *Schweiz. med. Wchschr.* **57**:525, 1927.
- Linder, W., and Morse, L. J.: Analysis of Eighty-Eight Cases of Acute Pancreatitis with Special Reference to Diagnosis, *Ann. Surg.* **90**:357, 1929.
- Love, R. J. M.: Treatment of Acute Pancreatitis (Hunterian Lecture), *Lancet* **1**:375, 1929.
- McWhorter, G. L.: Acute Pancreatitis, *Arch. Surg.* **25**:958 (Nov.) 1932.
- Menegaux, G.: Pathogenesis of Acute Pancreatitis; Origins of Pancreatic Necrosis, *Progrès méd.* **42**:2009, 1927.
- Morhardt, P. E.: Mechanism of Acute Hemorrhagic Pancreatitis, *Presse méd.* **36**:52, 1928.

- Myers, W. K., and Keefer, C. S.: Acute Pancreatic Necrosis in Acute and Chronic Alcoholism, *New England J. Med.* **210**:1376 (June 28) 1934.
- Nicolaus, H.: Methods of Treatment and Permanence of Cure of Acute Pancreatitis, *Beitr. z. klin. Chir.* **152**:351, 1931.
- Nordman, O.: Necrosis in Acute Pancreatitis from Cholecystitis, *Chirurg* **1**:721, 1929.
- Popper, H. L.: Diagnostic Value of Determination of Diastase Content of Blood and Urine in Acute Pancreatitis, *Deutsche med. Wchnschr.* **55**:1712, 1929.
- Roseno, A., and Dreyfuss, W.: Diagnosis of Acute Pancreatitis, *Deutsche med. Wchnschr.* **54**:783, 1928.
- Rostock, P.: Diastase in Urine in Acute Pancreatic Necrosis, *Beitr. z. klin. Chir.* **143**:330, 1928.
- Sarma, P. J.: Surgical Exposure of the Pancreas, *Am. J. Surg.* **21**:390 (Sept.) 1933.
- Seaglia, G.: Acute Hemorrhagic Pancreatitis with Stenonecrosis Caused by Abdominal Trauma, *Riforma med.* **46**:971, 1930.
- Scherk, G.: Difficulties in Making Differential Diagnosis of Cholelithiasis and Acute Pancreatitis, *Med. Klin.* **26**:1564, 1930.
- Schmieden, V., and Schening, W.: Surgery of the Pancreas, with Especial Consideration of Acute Pancreatic Necrosis, *Arch. f. klin. Chir.* **148**:319, 1927.
- Stocker, H.: Acute Pancreatitis—Necrosis: Clinical and Statistical Study, *Arch. f. klin. Chir.* **156**:84, 1929.
- Tammann, H.: Results of Surgical Treatment of Necrosis at Surgical Clinic in Göttingen from 1912-1929, *Beitr. z. klin. Chir.* **148**:49, 1929.
- Tracy, B. M.: Gallstones with Acute Pancreatitis at Age of 16, *Brit. M. J.* **1**:346, 1928.
- Unger, E., and Sostmann, H.: Experiences in 100 Cases of Acute Pancreatitis, *Med. Klin.* **27**:198, 1931.
- Valdes, U.: Clinical Aspects of Acute Pancreatitis, *Rev. Asoc. méd. mex.* **7**:18, 1928.
- Walzel, P.: Diagnosis and Treatment of Necrosis in Acute Pancreatitis, *Beitr. z. klin. Chir.* **147**:3, 1929.
- Wangenstein, O. H.; Leven, N. L., and Manson, M. H.: Acute Pancreatitis (Pancreatic Necrosis); Experimental and Clinical Study, with Special Reference to the Significance of the Biliary Tract Factor, *Arch. Surg.* **23**:47 (July) 1931.
- Weeden, W. M.: Acute Pancreatitis with Report of Twelve Cases, *Am. J. Surg.* **8**:1286, 1930.
- Weintrob, M., and Geshwind, M. H.: Acute Pancreatitis in Children, *M. J. & Rec.* **130**:154, 1929.
- Wohlgemuth, J.: Diagnosis of Necrosis in Acute Pancreatitis by Determination of Diastase Content of Urine, *Klin. Wchnschr.* **8**:1253, 1929.

# A REVIEW OF UROLOGIC SURGERY

ALBERT J. SCHOLL, M.D.

LOS ANGELES

E. STARR JUDD, M.D.

ROCHESTER, MINN.

JEAN VERBRUGGE, M.D.

ANTWERP, BELGIUM

ALEXANDER B. HEPLER, M.D.

SEATTLE

ROBERT GUTIERREZ, M.D.

NEW YORK

AND

VINCENT J. O'CONOR, M.D.

CHICAGO

(Concluded from page 907)

## PROSTATE GLAND

*Calculi.*—Franceschi<sup>27</sup> stated that it is only recently that a clear distinction has been drawn between urethral calculi and true prostatic calculi formed and grown primarily within the substance of the prostate. Since 1927 he has found only 16 cases of the latter in the literature. True endoprosthetic calculi may be either autochthonous (endogenous) or migrating (exogenous), the former being the more rare. Endoprosthetic calculi migrating from the urethra into the prostate, of which a case is here reported, are generally small and numerous but may occasionally be large and single, as in the present case, in which the form of the calculus confirmed its deep endoprosthetic situation by the faithfulness with which its arborization repeated the acinous structure of the organ within which it had developed.

The mode of exclusion of these calculi from the urethra may be conceived as the formation of a parenchymatous or interstitial reaction, with organization of granulation tissue, or there may be a purely mechanical factor of inclusion following fibro-adenomatosis, especially in men with a tendency to prostatism. The commonest type of stone formation is uric acid lithiasis, and the type of infection most frequently associated therewith is that which results from the enterococcus. The  $p_H$  seems to be more acid in this condition, with the presence of crystals of sodium urate or of free uric acid. These concretions are almost symptomless and are usually discovered at the time of prostatectomy. They

---

27. Franceschi, Eugenio: Contributo allo studio della calcolosi prostatica vera, Arch. ital di urol. 11:366 (June) 1934.

may escape detection in the roentgenogram, since uratic calculi have a composition similar to that of the soft parts of the body and are among those least visible roentgenographically, even on the best films, while calculi of pure uric acid may be invisible, especially if they lie deep within a parenchymal organ.

Endoprostatic calculi may be masked completely by prostatism until some congestive or infective factor favors their mobilization. In this stage they present the characteristic and marked sign of producing a grating sensation on introduction of the sound, a sign which may be regarded as pathognomonic. In Franceschi's case in a man 79 years of age, the remarkable feature was the fact that there had been no signs of prostatism until a few weeks before observation, when an attack of retention occurred, for which the patient treated himself with a retention catheter which he was wearing when he came in for treatment. It is probable that the irritation produced by the catheter was responsible for the mobilization of the calculus, which was found at operation and was removed by the suprapubic route. Franceschi regarded this approach as the safest, and he found valuable aid in incision of the neck of the bladder. This route gives the best guarantee of success with prompt and secure drainage, besides resting the bladder without exposing the patient to the risks of perineotomy, which may lead to the formation of fistulas and to recurrence, particularly if periprostatitis and rectal adhesions are present. When chronic prostatitis exists, a suprapubic prostatectomy is often the best mode of treatment.

[COMPILER'S NOTE.—In the surgical management of prostatic calculi, it appears that the perineal route of approach is surgically and anatomically the most convenient, since it is easier to expose the prostate gland and remove the calculi under direct vision without opening the bladder, thereby simplifying the procedure. Those patients who are subjected to a suprapubic operation for drainage of a prostatic abscess or for the removal of prostatic calculi are required to stay in the hospital much longer than those on whom a perineal operation is carried out for one of the same conditions. It has also been shown that the surgical shock is greatly diminished in the perineal operation and that the drainage from below is always more satisfactory, even when prostatectomy is to be done. It is evident, therefore, that in cases of prostatic calculi the procedure of choice should always be by the perineal route rather than by the suprapubic route.]

Hamer and Dykhuizen<sup>28</sup> stated that calculi found in the prostate fall into one of two main groups: the endogenous, which are formed in the prostate gland and, at least at their inception, never come in contact with the urinary constituents, and the exogenous, which are formed

28. Hamer, H. G., and Dykhuizen, T. A.: Prostatic Calculi, *Am. J. Surg.* **24**: 119 (April) 1934.

higher up in the urinary tract and are arrested in the prostatic urethra where they increase in size. The latter calculi cannot be regarded as true prostatic calculi since they originate outside of the prostate gland and are composed of urinary salts. These can be distinguished from true prostatic calculi which have eroded through the prostate gland and have acquired a secondary coating of urinary concretions by chemical examination of their nuclei. A true prostatic calculus has an albuminoid nucleus, whereas an exogenous calculus has a nucleus composed of uric acid, urates or oxalates. The true prostatic calculi are probably formed by deposits of calcareous material on the corpora amylacea, which are frequently met in sections of apparently normal glands. Prostatic calculi are found chiefly in adults, although in the series of 305 cases reviewed by Thomas and Robert, 4 boys aged 10 years had prostatic stones. These investigators found that two thirds of the patients were between 40 and 60 years of age, the greatest number being between the ages of 50 and 60. Hamer and Dykhuizen stated that several pathologic conditions are found associated with prostatic stones. Invariably there is a low grade of prostatitis; urethral strictures are relatively frequent; calculi in other parts of the urinary tract are frequently demonstrated; carcinoma of the prostate seems to be a rare accompanying lesion. True prostatic calculi are almost always multiple. Joly believed that the cases in which a single stone has been removed are examples of urinary stones that have become lodged in the prostate. Usually the smaller stones occur in such numbers and are so small that it is impossible to count them. There are recorded cases in which more than a thousand stones have been removed. The smaller stones are usually round and have no facets; they are dark brown and can often be cut with a knife. They are often scattered throughout the prostate gland and extend down the ducts and into the acini. These give a characteristic dotted appearance on the roentgenogram. The larger stones usually occur in pouches formed by the destruction of the glandular walls. Frequently these stones are faceted where they touch one another. The most common arrangement, as viewed on the roentgenogram, is a mass of stones in each lateral lobe connected by an isthmus. The distribution is not always symmetrical. Chemical analysis of the stones reveals that they are composed of an organic and an inorganic element. The organic material, which forms the nucleus, is of an albuminoid nature but is apparently not a true protein. The inorganic salts are calcium phosphate, potassium phosphate, magnesium phosphate, calcium oxalate and calcium carbonate. The changes in the prostate vary according to whether there has been suppuration and whether the stones have attained sufficient size to ulcerate through the gland. The gland is invariably enlarged but is rarely over twice its normal size. Its surface is firm and is usually regular, but at times it is nodular and hard. If the stones are large, the condition can be distinguished from

carcinoma of the prostate by the roentgenogram. Usually the border of the prostate is well defined in cases of calculi in contrast to the irregularity of the border in cases of carcinoma, and this aids in differentiating the two conditions by rectal examination. The roentgenogram is most important in making a diagnosis of prostatic calculi, but one should bear in mind the possibility of phleboliths in the prostatic plexus. Often, however, a presumptive diagnosis and less often a positive diagnosis can be made by other means. Sometimes prostatic stones are first suspected by the grating which they impart to an instrument passed into the urethra. Hamer and Dykhuizen stated that the treatment of prostatic calculi often will depend on the other conditions which are present. The frequency with which prostatic hypertrophy accompanies prostatic calculi makes the treatment of the former condition of primary importance, and the stones are of secondary interest. When the stones were small and very numerous the prostate was enucleated through the suprapubic route, and the resulting cavity was thoroughly explored and sponged. A surprising number of stones are recovered clinging to the dry gauze sponge, even after a thorough digital examination fails to detect them. Many operators prefer the perineal route for the removal of larger stones. The presence of small prostatic calculi does not contraindicate electrical resection or interfere appreciably with this procedure. On the contrary, it was found to be a satisfactory method of removing a subcervical nest of calculi in 1 case.

*Resection.*—Transurethral manipulations and operations have substantially transformed urologic practice. Conservative management of lesions of the upper part of the urinary tract, such as relief of infection, stasis, technical expulsion of stone, relief of certain hematurias and correction of ureteral drainage defects, proclaims its effectiveness. It has even a greater field in cases of lesions of the bladder and of the lower part of the urinary tract, and its application in recent years for all types of obstruction of the neck of the bladder has revolutionized prostatic surgery.

Caulk<sup>29</sup> has performed 900 transurethral prostatic resections with his cautery punch, with an operative mortality of 1 per cent. He emphasized the necessity for repeated operations in cases of the larger prostatic hyperplasias and stressed the marked retrogression and shrinkage in the remaining portion of the gland following partial resection.

He emphasized the advantages of the punch operation with the cautery current over the more commonly employed electroresection with the high frequency current. To the destructive effects of the latter he

29. Caulk, J. R.: Transurethral Surgery, Surg., Gynec. & Obst. 58:341 (Feb.) 1934.

attributes most of the hemorrhage, infection, sepsis and toxic absorption which not infrequently follow electroresection.

To study the effect on tissues and the heat-penetrating properties of various electric currents, extensive and elaborate experimental studies on both animals and human beings were undertaken. A standard thermocouple galvanometer was used to record the temperature of the tissue. The deductions reached were:

1. High frequency currents generate heat in the tissues at points distantly removed from the actual site of burning, often in a degree exceeding the thermal death point of the tissue cells.

2. The heat generated in the tissues by the cautery current never penetrates to such depths.

3. The coagulation currents producing pronounced superficial necrosis result in much less intense heat in the tissue than the cutting currents of higher tension values.

4. The cumulative effects of heat generated in the tissue may be partially combated by restriction of the duration of repeated applications of the high frequency current so as not to retard unduly the normal flow of blood through the prostate gland. This has been estimated to be 0.68 Gm. of blood per cubic centimeter of tissue per minute.

He concluded that the incidence of secondary hemorrhage and sepsis following resection with the high frequency current can be attributed to the erosive effect of late sloughing on the walls of the blood vessels as a result of the penetrating effects of the heat of the current. This cellular destructive effect is not present with the cautery method of resection, in which there is simply a superficial reaction.

It is of the utmost importance during the performance of resection with the high frequency current that currents of minimal tension value be employed, that the cutting action be performed expeditiously, that repeated resections at one point be avoided if possible, and that surface coagulation be utilized for the sealing of bleeding points. For these reasons, extensive and repeated resections necessitating a large number of applications of the current are to be condemned, since the accumulation of heat and subsequent destruction of tissue in the outer surfaces of the gland may be productive of late sloughing and erosion, with the development of urinary extravasation, the formation of a fistula and urinary incontinence.

A clinical study of the relative merits of the two methods was made through a questionnaire answered by 244 surgeons who had performed 15,488 transurethral operations, of which 7,415 were done by the punch method and 8,073 by electroresection. Analysis of the answers showed that the incidence of postoperative hemorrhage following electroresection exceeded that following the cautery method in the ratio of 2:1, and the

same proportion also applies to the necessity for cystotomy in its control. Urinary sepsis also occurred more frequently, the ratio being 2.5:1, whereas the incidence of other complications as a postoperative complication with electroresection, e. g., urinary incontinence, fistulas, prostatic abscess and rupture of the bladder, was also greater than with the cautery method; they occurred 39 times with the former and 9 times with the latter. It is of interest to note that the development of rectourethral fistula complicated the course following electroresection 5 times, whereas there is no record of this with the cautery operation.

Caulk concluded that the experimental and statistical study demonstrates the greater value of the cautery method of transurethral resection as compared to electroresection. He described a modification of his punch instrument which provides telescopic visualization of the operative field.

Garshwiler, Weyerbacher and Balch<sup>30</sup> stated that transurethral prostatic resection is a distinct advance in the management of obstruction of the neck of the bladder but that it should be used in selected cases. It is conceded that median fibrotic bars, carcinoma of the prostate, hypertrophy of the middle lobes and less extensive hypertrophy of the lateral lobes are ideal conditions in which to use resection. In cases of more extensive hypertrophy, especially of the lateral lobe, prostatectomy should be used. They stated that functional results have been very gratifying in their cases, with the exception of a few cases of enormous hypertrophy of the lateral lobes. Postoperative morbidity and complications have been conspicuously few and very mild. The authors have noted many more complications during preparation with catheter drainage than after resection. Their mortality has been 2 per cent.

From the standpoint of end-results, Goldstein and Herschman<sup>31</sup> stated that they have not met the same success that they have had in their cases in which prostatectomy was performed. There was a direct operative mortality of 10 per cent. Five of the 6 deaths occurred in cases in which the patients presented a poor surgical risk. The authors were able to operate on 18 patients who in all probability would not have been able to stand the surgical shock caused by an open major operation. In other words, 13, or 72.2 per cent, of these patients at the time of the report were living and comfortable without "leading a catheter life." Pyelonephritis is the complication most frequently encountered and causes a great deal of concern when present. The

30. Garshwiler, W. P.; Weyerbacher, A. F., and Balch, J. F.: *Transurethral Prostatic Resection: Study of Functional Results and Morbidity Following This Procedure*, *Urol. & Cutan. Rev.* 38:413 (June) 1934.

31. Goldstein, A. E., and Herschman, M. J.: *End Results in Prostatic Resection*, *Urol. & Cutan. Rev.* 38:410 (June) 1934.



authors' best results were obtained in cases of contracture of the vesical orifice and median bars.

Folsom and Alexander<sup>32</sup> stated that it was their opinion that prostatic resection, in the hands of competent operators, is destined practically to supplant the older types of surgical procedure. This view is based on their experience in 225 cases in which resection was performed. At the same time they had performed prostatectomy in only 3 cases, which means that they had been able to relieve 98 per cent of their patients during the past two and one-half years with this procedure.

Day<sup>33</sup> stated that prostatic resection, as developed during the past three years, has enormously widened the field of transurethral operations. Because it is spectacular and in the beginning seemed so simple and harmless, it resulted in widespread publicity even among the laity. Therefore the laity demanded it, even those persons with incipient prostatic hyperplasia who would have been better off without operation for the time being. Day expressed the belief that great gains have resulted from resection selectively employed and that its use should be encouraged and not abused. He stated that from 50 to 65 per cent of persons with adenomatous prostates fare better after prostatectomy than after resection and that the mortality after prostatic enucleation in comparable circumstances is certainly no greater and probably less. The post-resection morbidity and the deaths occurring in the succeeding six months stamp indiscriminate resection as unsound practice.

Sargent<sup>34</sup> stated that without any convincing exceptions each of the pioneers in resection has reported a substantial mortality in his early cases, whereas, with judgment and skill obtained by experience mortality practically disappeared. The very unanimity of that experience points to two conclusions. One is that resection without the benefit of adequate training under some one who is experienced is an extremely dangerous procedure. The other is that with experience resection comes to be both simple and safe. Sepsis is the outstanding danger. Here again is demonstrated the old observation that it is practically impossible to escape a certain amount of infection in operations on the bladder and that when the urinary tract is thus infected it demands drainage that is free, uninterrupted and adequately prolonged.

Weltman and Plaggemeyer<sup>35</sup> found that as one gains experience with the resectoscope, its field of usefulness greatly broadens. The

---

32. Folsom, A. I., and Alexander, J. C.: Report of Two Hundred and Twenty-five Prostatic Resections, *Urol. & Cutan. Rev.* **38**:400 (June) 1934.

33. Day, R. V.: Prostatic Resection: Its Comparative Evaluation, *Urol. & Cutan. Rev.* **38**:397 (June) 1934.

34. Sargent, J. C.: Resection of the Prostate: An Evaluation, *Urol. & Cutan. Rev.* **38**:394 (June) 1934.

35. Weltman, C. C., and Plaggemeyer, H. W.: Two Years' Experience with the Resectoscope, *Urol. & Cutan. Rev.* **38**:392 (June) 1934.

operator with sufficient experience and ability will be able to remove successfully practically all types of prostates transurethraly. The procedure is, and always will be, a difficult and laborious task, so filled with potential pitfalls that one must be constantly on guard. It is easy for the patient but difficult and tricky for the operator. Weltman and Plaggemeyer stated the belief that in the future, owing to the lessened risk to the patient, men with urinary obstruction will seek resection early before large amounts of residual urine accumulate and before severe infection and renal damage occur. The results will be much better. They stressed that in spite of the most meticulous care in pre-operative and postoperative handling the one outstanding thing that the expert resectionist has to guard against is infection.

Mathé<sup>36</sup> stated that at the present time the indications for transurethral resection are being defined. Enthusiastic urologists who have become expert in endoscopy employ the transurethral method for the relief of nearly all types of prostatic hypertrophy that come under their care. The following percentages indicate how widely some urologists are applying the procedure: Ballenger, Elder and McDonald, 95 per cent; at the Mayo Clinic, 98 per cent; Engel, 85 per cent, and Alcock, Kretschmer and Caulk, nearly 100 per cent. These surgeons use this method in cases of moderate hypertrophy, including hypertrophy of the median lobe with intravesical encroachment, bilateral lobular involvement and trilobular hypertrophy. Their writings indicate that they feel that open prostatectomy, a well established surgical procedure, is about to be discarded in favor of resection. Another large group of more conservative men, Lowsley, Collings and de Shivers, feel that this procedure should not be employed in the vast majority of cases of prostatic hypertrophy; they limit its use to cases of hypertrophy of the subcervical group of glands, cases of moderate bilobular and trilobular adenomas and cases of fibrosis connected with the collar type of hypertrophy or atrophy of the prostate. A third group feel that their experience with resection justifies its application in an increasingly large number of cases, from 80 to 85 per cent of all cases of prostatism, but they have pointed out that it is insufficient to give permanent relief in cases of an extremely vascular gland and no relief whatever in those cases in which it is mechanically impossible to pass the resectoscope or to perform resection of sufficient tissue without danger of perforating the prostatic capsule or the wall of the bladder. Mathé stated that with the improvement of technic on the part of the resectionist the percentage of cases in which resection can be successfully performed increases in direct proportion to the skill acquired, with

36. Mathé, C. P.: Further Observations in the Treatment of Prostatic Hypertrophy by Transurethral Resection. *Urol. & Cutan. Rev.* 38:381 (June) 1934.

the result that this method is unsuccessful in only from 5 to 15 per cent of cases of all types of prostatic disease. The contraindications to resection are: (1) inability to pass the resectoscope, which may result from congenital and acquired stricture of the urethra and vesical neck, and distortion of the prostatic urethra resulting from bizarre forms acquired by the hypertrophied prostate; (2) spongy hypertrophy in which instrumentation and resection cause extensive hemorrhage; (3) massive hypertrophy of the prostate; (4) hypertrophy complicated by diverticula and huge stones in the bladder; (5) contracted bladder (capacity under 150 cc.), and (6) cystotomy.

Mathé concluded that resection deserves a firm place among the operative procedures on the prostate gland. It has come to stay and its indications have been rather well defined. When properly performed, it will give satisfactory and lasting results in cases in which the patients are suffering from the collar type of fibrotic hypertrophy, atrophic sclerosis and moderate hypertrophy of the median and lateral lobes. It also affords palliative relief to the patient who presents a poor risk and who has massive hypertrophy or carcinoma of the prostate, in which case an open operation is contraindicated. Mathé said that it does not supplant prostatectomy, which should be employed in cases in which there are massive hypertrophy and spongy bleeding. Prostatectomy should likewise be employed in all cases in which instrumentation is hazardous by reason of a severe reaction on the part of the patient or because of urethral stricture, pathologic deformity of the anterior and posterior urethra and marked contraction of the bladder. Open operation is also indicated in cases in which there are complicating diverticula and huge stones of the bladder and in those in which it has been necessary to perform cystotomy. Transurethral resection of the prostate is a highly technical procedure that is difficult to learn and can be performed skilfully only after the development of proper technic. In skilled hands, uniformly good results have been obtained, and the mortality has proved to be lower than with prostatectomy.

Ballenger, Elder and McDonald,<sup>37</sup> who have had twenty-five years of experience with prostatectomy and who have employed transurethral resection 290 times on 227 patients, have compared their results with each of these procedures and have found that the comparison strongly favored transurethral resection. Four of the patients who were subjected to resection died: 2 from heart failure, 1 from uremia and 1 from pneumonia. Considering the greatly enfeebled condition of many of

---

37. Ballenger, E. G.; Elder, O. F., and McDonald, H. P.: Analysis of the Results of Two Hundred and Ninety Transurethral Prostatic Resections, *Urol. & Cutan. Rev.* **38**:407 (June) 1934.

the patients who were subjected to resection, the authors felt that had they been subjected to prostatectomy, either in one or in two stages, the mortality probably would have been five times greater. In fact, many of the patients would have been regarded as too feeble to withstand prostatectomy. This group includes all of the operable patients who had prostatic obstruction, except 2 for whom prostatectomy was employed because of the large size of the hypertrophied mass. The average age of the patients was 64 years; the oldest patient was 86 years of age. The time required in the hospital after the resection for 90 per cent of the patients was five days. Hemorrhage is probably the most important complicating factor in resection. Patients vary greatly as to the amount of bleeding which occurs. Extra care should be taken in checking oozing and bleeding in cases in which there has been a fall in blood pressure, even though considerable time may be required in the operating room for the caffeine, sodium benzoate and other remedies to raise the blood pressure. Late bleeding was not of infrequent occurrence, especially during the second and third weeks after operation. This nearly always responded to rest, free intake of fluids and medication. In no case were hemostatic bags employed, nor was suprapubic cystotomy required or done for the control of bleeding at the time of resection or later. As a rule the bleeding varied with the size of the gland, although many patients who had hypertrophy of considerable size bled very little; this was in cases in which the tissue cut like potato. Bleeding should always be expected; at least, all precautions should be taken to have every part of the equipment in thorough working order and the patient adequately anesthetized so that he is quiet and does not strain or try to move. Low spinal anesthesia is the method of choice. It is kept low by using a solution containing procaine and strychnine, which is lighter than the spinal fluid, and by tilting the head of the table downward before injecting the solution. The table is kept level while the needle is being inserted. When the needle is properly placed, the head is lowered, and not until then is the injection made. The sexual function, as a rule, is not impaired by prostatic resection; sometimes it is improved; at other times it remains the same as before the operation. In this series none of the patients had incontinence, and Ballenger, Elder and McDonald stated that they had no fear of it because they took such extreme care with all cuts near the verumontanum. The good results already obtained, however, by those doing a large number of resections, the low mortality, the small amount of pain incident to the procedure and the short time needed for postoperative hospitalization have already proved that the procedure is a definite improvement over prostatectomy.

*Carcinoma.*—Stirling<sup>38</sup> stated that the treatment of prostatic malignant conditions consists in the radical procedures of prostatectomy with radium implantation and roentgen irradiation of the prostatic region in cases in which the growth is confined to the capsule and in which urinary obstruction is present. If there is no obstruction, radium implantation and roentgen irradiation may be used. When the malignant growth has extended beyond the prostatic capsule, as had happened in the majority of cases when diagnosed, radical surgical measures rarely effected a cure, and the procedure to be followed is either punching out or resecting the obstruction; this should be repeated as needed to insure the patency of the urethra. Radium and roentgen therapy should be used to stop pain and bleeding. These agents will often retard the growth and cause a marked improvement in the patient's condition. Before any operative procedure is undertaken for carcinoma of the prostate, a preliminary roentgenologic study should be made, including cysto-urethrogramms to determine the type of tumor, its location and extent and whether metastasis has supervened.

*Sarcoma.*—Gilbert<sup>39</sup> reported 2 cases of sarcoma of the prostate gland which affected youths and reviewed the recent literature to determine the value of irradiation in the control of this disease. Both cases demonstrated unusually difficult diagnostic problems and were regarded as infectious. Thus, emphasis was laid by Gilbert on the differentiation of sarcoma and prostatic abscess. In 75 per cent of the cases the growth occurs before the generally accepted age for carcinoma of 40 years, and in about 80 per cent of cases it occurs before the usual age for prostatic adenoma. The highest age incidence is between 1 and 10 years; about 30 per cent of the patients are between these ages. Pain may be located deep in the pelvis and may be constant; it may be related only to the intestine or to the urinary tract. It usually extends to the sacral region and posteriorly down the legs. Hematuria is a variable and unreliable symptom. It depends on ulceration of the primary tumor into the bladder or posterior urethra and is rare among children as the rapidly growing mass frequently produces obstruction much earlier in the course of the disease. The preoperative diagnosis of sarcoma of the prostate is rarely made, possibly because it is known to be rare and is seldom considered. The onset is usually insidious, and the symptoms are not uniform. The soft doughy feel of the tumor commonly leads to a diagnosis of simple cyst, echinococcus cyst, hypertrophy and occasionally carcinoma. Widespread metastasis occurs early, and thorough

---

38. Stirling, W. C.: Treatment of Prostatic Cancer, *South. M. J.* 27:590 (July) 1934.

39. Gilbert, J. B.: Sarcoma of the Prostate: Report of Two Cases, *J. Urol.* 32:63 (July) 1934.

roentgenographic studies of the chest and bony structure (skeleton) should be made as a routine measure as they are when carcinoma is suspected. The incidence of metastasis to the lungs as well as to the bones was 33 per cent in Smith and Torgerson's series of 34 cases. In other cases the tumor has filled the whole pelvis, extending superiorly to the umbilicus. The contour is usually regular but not always smooth and is of a peculiar firm consistency, which is described as "boggy." Its consistency resembles that of a gland which has been chronically infected. It follows that the more rapid the growth of the tumor in younger patients, the less dense is its consistency. Gilbert stated that a variety of surgical procedures have failed to control the disease adequately. He believed that surgical intervention was indicated only to relieve obstruction and in the treatment of complications. Complete prostatectomy is seldom possible as the tumor is only rarely found to be limited within the capsule. Irradiation, both theoretically and clinically, offers a greater chance to control this disease. Adequate intensive irradiation by means of gold radon implants and high voltage roentgen therapy, preferably by the Coutard technic, is advocated primarily in all cases. Clinical control in between two and six years has been obtained in cases in which the patients were more than 40 years of age. In the case of young patients, however, the average extension of life has been six months. A review of results in the recent literature indicated the superiority of irradiation over any type of surgical procedure. This disease, when treated by surgical methods, has been uniformly fatal. Bettoni reported that after twenty radical operations 75 per cent of the patients had recurrences in two or three months. Smith and Torgerson record that 14 of a total of 84 patients lived two and one-half months or less after the onset of symptoms. They concluded that the round cell type of tumor is the most malignant; in 30 cases recorded, the average duration of life was one hundred and forty-four days. The percentage of other types of tumors was so small that their relative degree of malignancy could not be correctly estimated. However, it may be assumed that the spindle cell type, along with the other less cellular tumors, is less malignant.

#### URETHRA

*Trauma.*—Ormond and Cothron<sup>40</sup> described a case of fracture of the pelvis with complete severance of the urethra just anterior to the prostate gland. Suprapubic cystostomy and insertion of a Pilcher bag, after the passage of a sound through the urethra and subvesical space

---

40. Ormond, J. K., and Cothron, R. M.: A Simple Method of Treating Complete Severance of the Urethra Complicating Fracture of the Pelvis, *J. A. M. A.* 102:2180 (June 30) 1934.

with the assistance of a finger in the opened vesical neck, served to approximate the torn ends of the urethra and to obliterate the void between the segments. The bag was left distended for two weeks and was then withdrawn; an indwelling catheter and suprapubic drain were left in for several days longer. The suprapubic wound healed quickly, and normal urination was effected in three days. The authors expressed the opinion that this procedure is rapid and avoids perineal section with its possible danger to future sexual function and almost unavoidable urethral stricture.

#### TESTES

*Undescended Testes.*—Aberle and Jenkins<sup>41</sup> stated that the anterior pituitary-like principle from the urine of pregnant women caused the testes to descend in 2 of 4 boys who received injections. In only 1 instance was the descent complete. The substance caused hypertrophy of the scrotum and testes and in 1 instance growth of the penis. In immature monkeys which had been subjected to unilateral orchidectomy, this hormone caused complete descent of the testes in 1 animal and partial descent in 4. In these 4 animals the fascia surrounding the vas deferens and spermatic vessel was too short to allow the testes to reach the lower part of the scrotum. The failure of the treatment may have been the result of an incorrect amount of hormone, of age, of nutrition or of some factor related to the activity of the other endocrine glands. In the case of man, possible external mechanical obstruction and developmental irregularities must be considered. Microscopic examination of the testes of the monkeys which had received injections of the hormone revealed marked tubular enlargement and a corresponding increase in interstitial material but no mature sperm. Identical amounts of the anterior pituitary-like factor caused various degrees of hypertrophy in the prostate, seminal vesicles and testes of immature monkeys. The total dosage of the principle administered is not in direct proportion to the distance that the testes descend either in man or in monkeys.

Engle first described the experimental production of descent of the testes in immature monkeys by the injection of hormones of the anterior pituitary body or of substances obtained from the urine of pregnant women. Cohn<sup>42</sup> stated that the incidence of undescended testis among army recruits is reported as varying from 2 to 5 per thousand applicants. The right side is more frequently affected, and the condition is bilateral in about 25 per cent of cases. Engle gave

---

41. Aberle, S. B. D., and Jenkins, R. H.: Undescended Testes in Man and Rhesus Monkeys Treated with Anterior Pituitary-Like Principle from Urine of Pregnancy, *J. A. M. A.* **103**:314 (Aug. 4) 1934.

42. Cohn, Samuel: Anterior Pituitary-Like Principle in the Treatment of Maldescent of the Testicle, *J. A. M. A.* **103**:103 (July 14) 1934.

a brief and sketchy résumé of certain published results which suggest that the operative treatment for maldescent of the testes is unsatisfactory in from 20 to 68 per cent of cases.

Lower and Johnson, working with normal adult rats, found that the injection of the gonad-stimulating hormone of the anterior pituitary body resulted in stimulation of the testes, as well as of the prostate gland and seminal vesicles. Other similar experiments indicate that although the testes did not appreciably increase in weight, the accessory organs increased markedly under the influence of the gonad-stimulating hormone, attaining the size characteristic of these organs in young adults. Evans repeated these experiments, but he said in addition that the testes themselves actually decreased in weight and seemed to be damaged by the treatment. Other work showed that anterior pituitary-like substance accelerated spermatogenesis and increased the size of the testes in immature rats.

Engle's work with monkeys formed the stimulus for Cohn's application of this principle to human beings. Six cases are reported in which 100 rat units of a commercial preparation (a purified form of the anterior pituitary-like sex hormone from the urine of pregnant women) was given subcutaneously three times weekly for ten injections. Cohn concluded from this small group of patients that this preparation is apparently effective in causing descent of undescended testes when there is no anatomic malformation to act as a mechanical obstruction. When an obstruction exists, a partial descent will occur, but operation will be required to complete the process. In surgical cases, the anterior pituitary-like principle is a valuable adjunct in the production of a successful outcome. In 4 otherwise normal children Cohn produced complete descent of one testis in 3 and only partial descent in the fourth, who, he stated, showed evidence of mechanical obstruction and will require operation.

To overcome the disadvantages of the Torek operation and to provide greater postoperative comfort and a shorter period of disability from the operation, Wolfson and Turkeltaub<sup>43</sup> have modified the technic as follows: Over the inguinal canal, hockey stick incisions, beginning at the pubic area, are made through the skin and the aponeurosis of the external oblique muscle. The broken lines are directed outward and upward. The external abdominal ring is split through at the middle of the intercolumnar fibers. The blades of the aponeurosis are separated widely to permit more mobility and better relaxation of the arched fibers of the internal oblique and transverse muscles. The gubernaculum testis should be identified and traced to

43. Wolfson, W. L., and Turkeltaub, S. M.: A Modified Torek Operation, *Am. J. Surg.* 25:494 (Sept.) 1934.



the lower attachment, which is then doubly clamped low down, cut and tied at both ends. The testis is palpated, viewed and appraised. Usually, it is covered with a veil of cremasteric muscle, from which it must be lifted. The testis and the spermatic cord are now gradually withdrawn from the inguinal canal. A finger dissection will mobilize this structure from its bindings of cremasteric muscle, adhesions and transverse fascia by starting posteriorly and working deep and high up into the retroperitoneal space. The vaginal process or peritoneal tube is freed from the vas deferens and spermatic vessels of the cord. The cord may be lengthened by separating all peritoneal remnants and adventitious tissue between the vas deferens and the spermatic vessels as far down as the testis and epididymis. The new bed for the testis is prepared by forcing a finger to the bottom of the scrotum. The base of the scrotum is next grasped with two Allis forceps 2 cm. apart. A transverse slit is made through the skin and dartos between the clamps. Another incision, parallel to, but lower than, the first and of equal length, is made on the inner and upper part of the thigh, facing the scrotum. The structures of the cord are correctly aligned. The length and the position of the testis in the scrotum are noted. If satisfactory, a clamp is passed through the scrotal incision to grasp and withdraw the free end of the gubernaculum testis through the scrotal slit. The testis is carried to the bottom of the scrotum. A union of the upper skin flap in the thigh to the posterior skin flap of the scrotum is then established with interrupted sutures. The gubernaculum testis is sutured to the newly formed posterior skin suture line with interrupted sutures of fine silk. The anterior and complete closure of the skin wound is then effected with silk sutures, which also incorporate the gubernaculum testis to this union. The inguinal canal and structure are reformed and reunited with sutures of no. 1 catgut. The spermatic cord should not be displaced. Two weeks after the orchiopexy the patient resumes his physical activities. Two months later the scrotum is detached from the thigh by an incision around the circumference of the scar and through the gubernaculum testis. A few interrupted sutures close the wounds of the two surfaces. This operation has been performed with satisfactory results in 45 cases of maldescended testis.

*Tumor.*—Salmon and Contiadès<sup>44</sup> reported a case of fibroma of Morgagni's hydatid in a man, aged 55. The small, solid, pediculate tumor, about the size of a hazelnut, was inserted at the anterosuperior pole of the right testis, where it had undergone fibrous degeneration with torsion. Histologically, it was a pure fibroma which did not

---

44. Salmon, Michel, and Contiadès, X. J.: Fibrome de l'hydatide testiculaire de Morgagni, *J. d'urol.* **37**:412 (May) 1934.

contain any muscle fibers but did contain an abundant formation of collagenic tissue which was in a state of inflammation. A search of the literature revealed no previous instance of any tumor that had been recognized as a pediculate fibroma of Morgagni's hydatid, but in several cases certain facts were reported which gave rather clear evidence of such origin. Glass reported a case similar to this in which on opening the tunica vaginalis for a slight effusion, a small pediculate, cellular fibroma, 5 cm. in length, was found resting on the albuginea. The structure of this tumor was beyond question the same as that of the one reported, but its topography is left in doubt since there was no mention of the insertion of the pedicle. It appears entirely possible, however, that it was a fibroma of the hydatid of Morgagni. In the case which was reported by Lavenant, a white foreign body, the size of a bean, was observed within the tunica vaginalis, which was causing severe attacks of pain, while the testis and epididymis were normal. Lavenant suggested the hypothesis that the structure was derived from some such embryonal débris as the hydatid, Germalde's body or the vas aberrans of Haller, which was in a state of chronic inflammation. Before the formation became a floating body it seemed to have possessed a pedicle, of which the hilus that was discovered was the last remaining trace. In the case here presented the operative findings revealed the insertion of the fibroma into the subepididymal furrow in the place of the normal hydatid, suggesting that it was a fibroma of the latter. The case is no doubt exceptional since the only previous observations at all comparable with it have been the result of purely anatomic findings and often have been incomplete and disputable. Clinically, the diagnosis may be suspected if the tumor is not too large. The most important points to observe are the connections of the tumor and its topography and mobility. Its opacity can be demonstrated by the absence of transparency when transillumination is carried out with a focus of light of small size and in a dark chamber. If the conception of a solid tumor situated under the head of the epididymis is then reached, it is justifiable to think of the possibility of an origin in Morgagni's hydatid, even though the greater probability is that of a polyp of the tunica vaginalis. The proper treatment of such a pediculate tumor consists of its extirpation, together with resection of the tunica vaginalis if there is any considerable serous effusion. It is possible that cases of this kind are, after all, not so rare as they seem, owing to the fact that at their outset the tumors exhibit no symptoms of any importance.

Henline<sup>45</sup> stated that the diagnosis of malignant tumors of the testis may be definitely made by determination of the presence of the

45. Henline, R. B.: The Differential Diagnosis and Treatment of Tumors of the Testicle with Report of a Case of Bilateral Fibroma of the Testes, *J. Urol.* 32:177 (Aug.) 1934.

anterior hypophyseal sex hormone in the urine by the Zondek method. The pathologic type of tumor may be determined before operation by the quantitative estimation of the excretion of this hormone. Local recurrences or metastasis may now be determined, even before clinical detection of the lesion is possible, by the reappearance or increase in the amount of the hormone excreted. The effect of irradiation of a testicular tumor on the excretion of this principle determines its radiosensitivity; thus, proper treatment may be outlined early in the course of the disease. Castration in the adult male may produce little or no change in his secondary sex characteristics.

#### SEMINAL VESICLE

*Carcinoma.*—Pelagatti<sup>46</sup> has added the report of an additional case to the 7 cases of undoubted malignant growth of seminal vesicular origin which he found reported in the literature. The only symptom experienced by the patient, a man aged 30, was obstinate constipation. Abdominal palpation revealed a nodule the size of a walnut on the left side and another, the size of an orange, a little nearer the left colic angle, while rectal palpation at the level of the prostate revealed an enormous mass which filled the entire small pelvis. The neoplasm, which was judged to be a tumor of the prostate, was considered inoperable, and the patient was sent home. Nine months later he was seen again, and at this time, in a frenzy of despair, he committed suicide.

At necropsy, metastatic nodules were found in the liver, pancreas, spleen and peritoneum of the transverse colon. There was infiltration of the lymph nodes of the mesentery of the small intestine and also of the perigastric, peripancreatic and pericolic lymph nodes. Nodules as large as hen's eggs were scattered throughout the liver, and the fatty capsule of the liver was infiltrated with neoplastic plugs. There was no invasion of the kidneys, suprarenal bodies or ureters, and the only vesical lesion was the presence of two superficial ulcerations of its mucosa on the posterior wall. The prostate, rectum, testes or vasa deferentia did not suffer in any way.

Behind the bladder, however, between it and the rectum, was a large round, whitish mass, the size of an infant's head invested with peritoneum and surrounded with other smaller nodules of the same character. On incision of the retrovesical peritoneum the mass was seen to be a part of the right seminal vesicle and ampulla. These, when cut, had an almost triangular shape with two distinct surfaces: an anterior or vesical surface, which looked normal and nearly flat and

---

46. Pelagatti, V.: Adeno-carcinoma della vescichetta seminale destra, Arch. ital. di urol. **11**:201 (Feb.) 1934.

which was not related to the tumor, and a posterior surface, which was folded in an angle with the vertex inward, becoming fused in the neoplastic mass. The lumen of both the seminal vesicle and the ampulla were, however, conserved and only slightly reduced. There were no changes in the left vesicles and ampulla. The prostate seemed rather small and was not involved in the mass.

The pathologic changes in the right ampulla were only slight and were chiefly the result of compression. Only at the vertex of its posterior surface were the muscularis and adventitia thickened and continuous in an indistinct way with the stroma of the tumor. The mucosa of the right seminal vesicle revealed a riotous proliferation of epithelial cells, especially in the posterior part, where no special structure was any longer discernible. In places not even the stroma supporting the mucosa could be recognized; there was only a great quantity of chaotic epithelial cells forming a sort of cord or plug leading into and becoming confused with the parenchyma of the tumor. Beyond the seminal vesicle the structure of the tumor was more glistening, with irregular trabeculae of collagenous fibers, which were ramified extraordinarily. The metastasis to the liver and lymph nodes faithfully reproduced the carcinomatous structure of the primary tumor. There was evidence that the metastasis was mostly by way of the lymphatics, but metastasis by the blood stream cannot be excluded, since there was manifest neoplastic infiltration of the walls of the newly formed vessels.

#### URINARY CALCULI

Thomas<sup>47</sup> stated that India may be looked on as the home of urinary calculi. Urinary calculus is one of the commonest conditions with which a surgeon is called on to deal. Two hundred and fifty cases were handled in a period of six years in a part of India in which this condition is very prevalent. The greater number of the patients were males who were more than 8 years of age. It was, however, a common thing to operate on much younger children. The youngest child was 6 months old and had a stone the size of a hazelnut. The proportion of females was small, and those operated on were chiefly below the age of puberty. The reason for this is obviously the ease with which small stones can be passed through the female urethra. Two or three cases of stone in the prolapsed bladder occurred among patients who had procidentia, the stones being removed through the anterior vaginal wall. A good many stones impacted in the male urethra were dealt with, the greater number being held up at the commencement of the penile urethra.

---

47. Thomas, R. C.: Stone in the Lower Urinary Tract in India: Examples of Multiple Calculi, *Lancet* 2:193 (July 28) 1934.

A small number of prostatic stones were encountered. The most common stone was the hard, smooth, oval uratic stone; two of these were often found and sometimes three. Next came the phosphatic stone. Both of these types were often very large. The mulberry calculus was always small, as the patient sought advice early because of the pain and vesical irritability it caused. Hematuria and pain at the end of micturition were the usual symptoms in cases of mulberry calculus. The other patients complained more of frequency, sudden cessation of the urinary flow and a feeling of heaviness in the perineum. Pain became a predominant symptom only when cystitis was present or when a stone became impacted in the prostatic urethra. Thomas stated that a striking thing about most of the cases was the long time during which symptoms had been endured before advice had been sought. Some of the adults, judging by the size of the stones, must have suffered for years. This was borne out by the multiplicity of stones in some cases. In several cases of long standing drainage of the bladder was necessary on account of the pronounced degree of cystitis. Thomas removed every stone by the suprapubic route except those in the prolapsed bladder and the impacted urethral stones. Many of the stones were very large and therefore not suitable for lithotripsy. Many patients had two and even three stones, and lithotripsy would have been a long operation. Cystitis was very common. The removal of a stone or stones by the suprapubic route never required more than twenty minutes, thus saving valuable time, and often it was completed in ten minutes. There appeared to be no more risk with the suprapubic operation than with lithotripsy. The suprapubic operation had the added advantage of permitting direct inspection of the vesical wall. The average time spent by the patient in the hospital was fifteen days. In India, time is of little account. All patients received a mixture of methenamine and acid sodium phosphate, 10 grains (0.65 Gm.) each, for three days, and the stones were removed on the fourth day. The operative technic consisted of the usual subumbilical incision and separation of the rectus abdominis and pyramidalis muscles, which were retracted by an assistant. The peritoneum was then wiped upward off the bladder, which was opened below it. After removal of the calculus, the bladder was swabbed dry and then closed from above downward with a running suture of no. 0 catgut, which included both mucous membrane and muscle. After this suture had been tied below, it was brought up again as an invaginating suture and tied with the original end. The fascia was closed with no. 1 catgut in children and no. 2 catgut in adults. The skin was closed with clips. A catheter was passed and secured in the usual way and retained for from nine to ten days.

Colby<sup>48</sup> stated that the fundamental problem in the consideration of urinary calculi is the prevention of recurrence. The importance of this statement is borne out by reports from the great clinics of the country of recurrences in from 20 to 40 per cent of the cases of nephrolithiasis. He emphasized the fact that stone in the kidney as well as stone in the bladder may be a sign of hyperfunction of the parathyroid glands rather than a primary urologic disease. The question of the formation of calculi is complex, and many factors must be considered. The urine itself presents the extraordinary phenomenon of an extremely supersaturated solution which does not obey the ordinary laws of chemical solutions. Substances excreted by the kidneys are but slightly soluble in water, for instance, uric acid and calcium oxalate; uric acid is from ten to twenty times more soluble in urine than in water. The ability of the urine to hold these salts in solution is said to be the result of the presence in the urine of protective colloids. They prevent the precipitation of the salts and inhibit the formation of calculi. If the colloids are deficient in amount, or if their action is interfered with by chemical changes, such as occur in stagnant urine, the protective mechanism is lacking, and the excess of free salts is precipitated as calculi. By feeding oxamide to rabbits and dogs, Keyser demonstrated that a marked increase in the crystalline content of the urine at times apparently so adds to the burden put on the colloids that they are unable to perform their protective action. Formation of calculi in the urinary tract is the result of an abnormal precipitation of the crystalline elements normally present in urine. There is much evidence to show that obstruction plays an important part in the formation of calculi, and all investigators regard urinary stasis as fertile soil for the subsequent formation of stones. The importance of infection as a cause of calculi is difficult to evaluate. Many stones develop in uninfected urine, and in many instances of long-standing sepsis calculi never occur. Urea-splitting organisms may cause rapid incrustations in the kidney and bladder. Diets deficient in vitamin A, if given for some time, cause crystalline deposits in the urinary tract of laboratory animals. The geographic incidence of stone, as in India and China, seems to be the result, in part at least, of dietary deficiency.

It has been proved that the parathyroid glands affect calcium metabolism. Total extirpation of these glands causes a decrease in the level of serum calcium and results in tetany. Tumors of the parathyroid glands cause marked metabolic changes with a loss of bone calcium, elevation of the level of serum calcium and an increase in the urinary output of calcium. The resulting bony changes, decalcification, cysts,

---

48. Colby, F. H.: *Urinary Calculi Associated with Parathyroid Disease*, Surg., Gynec. & Obst. 59:210 (Aug.) 1934.

benign giant cell tumors and spontaneous fractures, characterize the condition known as generalized osteitis fibrosa. The frequency with which stones occur in this disease is more than a coincidence.

In 28 cases of generalized osteitis fibrosa (Rankin), renal calculi were present in 5, and in 4 other cases in which tumors of the parathyroid glands were removed renal stones were present. The pouring out of calcium through the urinary tract seems to result in the formation of calculi in many patients with hyperparathyroidism. Urinary stasis is probably an important contributing factor in this condition. Tumors of the parathyroid glands have been removed from 13 patients at the Massachusetts General Hospital. In 8, or 61 per cent, demonstrable calcification was present in the urinary tract. Three had bilateral renal stones. The patients on presentation gave the usual history of renal colic, hematuria and other signs typical of stone in the kidney and without the usual symptoms of generalized osteitis fibrosa. The true condition in these patients was recognized by discovering a high serum calcium and a low serum phosphorus content. The output of calcium in the urine was increased and the output of phosphorus was decreased. Colby emphasized that while generalized osteitis fibrosa is frequently accompanied by urolithiasis it is important to recognize that calculi often form in the urinary tract without any of the bony changes which characterize this disease, although tumors of the parathyroid glands are present and constitute the underlying cause of the urolithiasis. Unless the tumor is removed the stones will frequently recur.

Keyser<sup>49</sup> cited the following facts as evidence that a metabolic disturbance may cause urinary calculi: 1. Calcium phosphate calculi developed in rats which were fed a diet that was deficient in vitamin A. 2. "Intensely excessive excretion of normal urinary crystalloids produces stone formation." Keyser and other investigators have demonstrated that artificially produced excessive oxaluria will cause urinary calculi under aseptic conditions. 3. "Crystalloids normally foreign to the urinary tract excreted therein by metabolic perversion are often found clinically as calculi." Keyser previously demonstrated that aseptic calculosis of this type could be produced by feeding oxamide. 4. "Colloids normally absent in the urine when they do find entrance may give rise to stone formation." The fibrin calculus, which is composed of alternating layers of calcium phosphate and fibrin, and calculi which are composed of cystine, xanthine, indigo and urostealith, are examples of this type of calculosis.

The evidence of specific infection as another cause of calculosis is presented. To the experimental work of Rosenow and Meisser with

---

49. Keyser, L. D.: *The Relationship of Urinary Infections to Recurrent Calculi*, J. Urol. **31**:219 (Feb.) 1934.

streptococci and of Hager and Magath with *Bacillus proteus-ammoniae*, Keyser adds instances of experimental infectious calculosis in rabbits produced by vesical inoculation with strains of streptococci from 2 patients who had calculi. A review of the mechanism of the experimental formation of stones discloses that hyperexcretory calculosis is dependent on the modification of urinary crystals by the urinary colloids from isolated units to coalescent, spherical units. When such fusing spherical units are precipitated simultaneously with the jellying of irreversible urinary colloids to form the organic framework, the formation of stones takes place. Calculosis from infection seems to arise from ulcerative lesions of the urinary epithelium and subsequent impregnation of this epithelium by lime salts.

Twenty-eight cases of recurrent urinary calculi were reviewed in detail. In 16 personal cases, almost all cases of alkaline earth stones with infection, Keyser has been able to break the cycle of recurrence by removal of existing calculi, by acidifying the urine with diet and drugs, by removal of focal infections and by repeated cystoscopic lavage and ureteral dilation to promote better drainage. In most instances this therapy has resulted in clearing up the urinary infection as well as in preventing the recurrence of calculi.

#### UROGRAPHY

Campbell<sup>50</sup> reported his observations in 381 intravenous urographic studies of 304 infants and children; in this study almost 1,900 urograms were analyzed. Two of the patients were 3 weeks old, and 2 others were 4 weeks old. There were 182 females and 122 males. Campbell employed the method in children for assistance in the diagnosis of chronic pyuria, of hematuria which was not the result of nephritis, of tumor or pain in or along the upper urinary tract and, in some instances, of disturbances of urination not falling under the foregoing groupings. Parenthetically, in practically every case in which a child has an abnormal excretory urogram or in which the results of ureteral catheterization suggest disease of the upper part of the urinary tract, a retrograde pyelogram should be made. Using the intravenous urographic mediums for instillation through a catheter, Campbell did not hesitate to perform bilateral retrograde pyelography. Retrograde urography was employed in all but 36 of the 304 cases and serves as a check on the intravenous method. Intravenous urography is particularly indicated in those cases in which ureteral catheterization is impossible or is refused or in which the condition of the patient does not warrant instrumentation. Campbell stated that this type of urog-

50. Campbell, M. F.: Intravenous Urography in Infants and Children: Observations in 304 Cases, *J. Urol.* 32:55 (July) 1934.



raphy is said to be contraindicated by severe renal or hepatic deficiency, idiosyncrasy to iodine, thyrotoxicosis, active pulmonary tuberculosis and exudative diathesis in children. Campbell used iopax 19 times, neo-iopax 8 times, skioldan 7 times, and diodrast 347 times. Iopax and skioldan are disadvantageous to inject because of the relatively large fluid bulk required; in highly nervous or unruly children this is a real disadvantage. Because of its freedom from irritating effect, as manifested by absence of pain in the arm on injection, and its minimal toxicity, rapid excretion and satisfactory concentration, Campbell preferred diodrast, particularly in children. The amount of solution required for children is relatively much greater than for adults. The average doses which Campbell employed for children were as follows (given in per cent of the adult dose): under 6 months of age, 25 to 30 per cent; 7 to 12 months, 30 to 35 per cent; 1 to 3 years, 35 to 50 per cent; 4 to 6 years, 50 to 80 per cent, and 7 to 8 years, 80 to 100 per cent. The child should be spared purging enemas until the return is clear, and starvation. Yet for constipated children a small dose of castor oil and a low enema to clear out the rectum are sometimes advantageous. No meal should be omitted; the longer the interval from the last meal, the greater will be the gaseous distention of the intestine. Greatly reducing the fluid intake for from twelve to eighteen hours before examination considerably increases the concentration of the excreted medium in the urine and thereby favors better urographic definition. For older children the injection is usually given into one of the cubital veins; for infants with fat arms and delicate vessels one may be forced to employ a superficial vein elsewhere (the wrist, the back of the hand, the feet or the scalp), the external jugular vein or, as Campbell did in 1 case, the fontanel. The injection should take at least two minutes; employment of a fine needle will control any tendency to too rapid injection. The conventional roentgenologic diaphragm can be used only for older cooperative children. For all others shorter exposures (from one sixteenth to one eighth of a second) must be employed. With the latter group, the roentgenologist must exert unusual patience and cooperation to make the exposure in the fraction of a second when the child is still; this is usually at one of the extremes of respiration and preferably at full expiration. As a rule, the interval between exposures is considerably less for children than for adults. The following schedule will be found satisfactory for most children: (1) flat roentgenograms made before intravenous injection; (2) injections of the radiopaque medium, and (3) roentgenograms made five, ten and fifteen minutes after the completion of the injection. The immediate development of the early roentgenograms will indicate whether longer or shorter intervals between exposures

will be advantageous; in some instances subsequent roentgenograms at intervals of an hour or more may be indicated.

Abeshouse<sup>51</sup> stated that the phenomenon of pyelolymphatic backflow can be graphically demonstrated by injection of the renal and perirenal lymphatics during pyelography. It was his opinion that injection of these lymphatics is the result of the easy penetration of pyelographic medium into anomalous renal lymphatics, which may be congenital or acquired. The presence of this type of anomalous renal lymphatics has not been demonstrated; this may be the result of the scant knowledge of the normal anatomy and physiology of the renal lymphatics, of dearth of pathologic specimens showing such changes and of the technical difficulties encountered in injecting normal and pathologic renal lymphatics. Overdistention of the renal pelvis and excessive pressure at the time of pyelography play no rôle in the production of injected renal or perirenal lymphatics. Abeshouse strongly emphasized the dire need of further investigation of the anatomy and physiology of the renal lymphatics and the necessity for careful pyelographic studies in cases of parasitic and nonparasitic chyluria of renal origin in order to demonstrate the exact point of communication between the lymphatic and the urinary system and to enhance the knowledge of the renal lymphatics.

#### ANESTHESIA

*Spinal Anesthesia.*—Spinal anesthesia, as employed by Howley and Robertson,<sup>52</sup> is comparatively safe and is usually preferred to general anesthesia in the urologic service at the Bellevue Hospital. In six years, spinal anesthesia was used in 1,490 cases. Two deaths were reported to have occurred in cases in which spinal anesthesia was employed; both patients presented a poor risk and were more than 70 years old. Patients who have hypotension or hypertension, with cardiovascular injury, present the poorest risks. Spinal anesthesia is not advisable for children or for apprehensive patients. Nupercaine (1:200) is best suited for long operations and procaine crystals are best for short procedures. A comparison between the results obtained in two periods of six years has been made from the same service with the same type of cases and practically the same attending staff. In one of these periods, which started in 1919, general anesthesia was used (gas-oxygen and gas-

51. Abeshouse, B. S.: *Pyelographic Injection of the Perirenal Lymphatics: Report of Two Cases and Review of the Literature; Consideration of the Relation of Pyelolymphatic Backflow to Chyluria, the Anatomy of the Lymphatics of the Kidney and the Mechanism of Backflow from the Renal Parenchyma and Pelvis*, Am. J. Surg. 25:427 (Sept.) 1934.

52. Howley, T. F., and Robertson, J. P.: *Spinal Anesthesia: Report of 1,490 Cases*, Am. J. Surg. 24:129 (April) 1934.

oxygen-ether) in 1,094 cases with postoperative death in 164, or 15 per cent. In the other period, which started in 1925, spinal anesthesia was used in a total of 1,490 cases, with postoperative death in 149, or 10 per cent. Although no attempt was made to prove anything, Howley and Robertson expressed the belief that the comparison is significant when one considers that each group of observations was from the same service with practically the same visiting staff and with the same type of cases.

#### PNEUMATURIA

Mulsow and Gillies<sup>53</sup> stated that pneumaturia without a fistula between the bladder and the intestinal tract is rare. The primary type of pneumaturia appears to be so rare and the condition persists for such a short time that few cases have been studied with any degree of completeness. The organisms which have been described in these cases have in all instances belonged to the colon group of bacteria. In the case reported by Mulsow and Gillies, *Nocardia* would not produce gas in urine or any of the ordinary carbohydrate culture mediums. It probably did not produce gas but was the only organism able to survive for any length of time in the strongly alkaline urine. None of the bacteria found in cases of pneumaturia has consistently produced gas in urine which was free from dextrose. Obstruction in the urinary tract, together with marked atony of the muscles of the bladder, has been found in most cases. In these cases there is often considerable residual urine and infection. In the case which was reported by Mulsow and Gillies it appears that the gas was formed either by the acid urine from the kidneys, which acted on the alkaline carbonates of the urine retained in the bladder, or by some organism which was killed by the strongly alkaline urine. The fact that no more gas was formed after the patient was placed on a diet for relief of ulcer and given alkalis suggests that the pneumaturia may have resulted from the action of the acids in the urine as it came from the kidneys. Other patients whose cases have been reported in the literature have recovered spontaneously or have been cured by simple rest in bed, antiseptic irrigations of the bladder and drainage of an infected kidney.

#### PRESACRAL SYMPATHECTOMY

McCrea and Macdonald<sup>54</sup> said that the functions of the autonomic nervous system are even now only beginning to be understood and that the knowledge of the nervous control of the bladder is incomplete.

---

53. Mulsow, F. W., and Gillies, C. L.: Primary Pneumaturia, with Report of a Case, *J. Urol.* **32**:161 (Aug.) 1934.

54. McCrea, E. D., and Macdonald, A. D.: Presacral Sympathectomy and the Urinary Bladder, *Brit. J. Urol.* **6**:119 (June) 1934.

Therefore, they warned against the too enthusiastic practice of presacral sympathectomy, because the indications for, and the results to be expected from, this procedure are not yet defined.

A vast amount of experimental work on animals has been done on the functions of the hypogastric nerves, which was summarized by Dennig in 1926. Since that time a number of observations on man have added to the knowledge acquired by the experimental physiologist. The authors have demonstrated that in the cat and the dog the effect of stimulation of any nerve trunk on intravesical pressure is conditioned by the muscle tonus and the nature and depth of the anesthesia and the bladder is inhibited by stimulation of the hypogastric nerves when in tone and showing rhythmic contractions. On decentralizing the viscus by spinal anesthesia, the inhibitor response is replaced by contraction. McCrea and Macdonald concluded that the hypogastric nerves contain both inhibitor and excitor fibers and that it has been too generally accepted that the sympathetic nerves of the bladder are purely inhibitors and the parasympathetic nerves are excitors.

On section of the hypogastric nerves in the dog it has been found that the bladder functions normally. When all the nerves but the hypogastric were divided, overdistention was still appreciated. Hyperemia also occurs as an effect of section of the presacral nerves, and pain is produced by stimulation of its central cut end.

The results of section of these nerves on the normal bladder of human beings are well known and do not differ from those noted in the bladder of animals. Micturition, thereafter, is absolutely normal, apart from occasional instances of slightly increased frequency. These nerves are not essential to a satisfactorily acting bladder. A number of observations have been made of the effect of section on the pathologic states of the bladder. The presacral nerve has been resected to relieve pain in cases of chronic cystitis, tuberculous cystitis, ulceration and "cystalgia." Pain can be partially but not completely controlled, and rebellious inflammations are sometimes cured, perhaps as suggested by Learmonth, because of vasodilatation.

The operation has been performed to relieve the retention of "cord bladder" in which it is assumed that the malfunction of the pelvic nerves results in unbalanced control of the hypogastric nerves. Improvement has been noted.

The authors concluded that the sympathetic and parasympathetic nerves function together in the regulation of the bladder but that the parasympathetic nerves, through the pelvic nerves, are by far the more important. While one or the other group may be the dominant excitors or inhibitors, yet it is not to be assumed that either is exclusively so or yet that they are antagonists. Both transmit sensory impulses, the

pathway of the pelvic nerves being the more important. The precise action of the hypogastric nerves on the vesical sphincter is unknown; in fact, they may not influence it at all.

#### UROGENITAL INFECTION

Walther and Willoughby,<sup>55</sup> who have had seven years of experience with azo dyes, found them of definite value in combating urogenital infections. These drugs, especially pyridium, have proved superior to the older urinary antiseptics in common use and are practically harmless in their action. They have a wider field of usefulness by acting equally well in alkaline or acid urine; they are synergistic to most other remedies and require no special dietary regimen. Notwithstanding the great practical value of combined clinical and laboratory research, Walther and Willoughby believed that there would remain much in the empirical inheritance of the dyes which would not be fully explained by present-day investigation.

---

55. Walther, H. W. E., and Willoughby, R. M.: Oral Dye Therapy in Urogenital Infections, *Am. J. Surg.* **25**:460 (Sept.) 1934.

# INDEX TO VOLUME 30

- Abbott, A. C.:** Effect of pneumothorax and oleothorax on histologic structure of thyroid, 667
- Abdomen:** See also Peritoneum  
 drainage; peritoneal drainage: resistance of sinus tract to infection, 1032  
 penetration of moist heat applied to abdomen and its effect on intestinal movements, 1036
- Abnormalities:** See also under names of organs and regions, as Kidneys, horseshoe; Penis, absence; Sacrum, absence; Spine, abnormalities; etc.  
 congenital deformities and disturbances of growth, 716  
 median cleft of lower lip and mandible, cleft sternum and absence of basihyoid, 647
- Abscess:** See also under names of organs and regions, as Brain, abscess; Lungs, abscesses perinephritic, 886, 887
- Achlorhydria:** See under Stomach
- Adelstein, L. J.:** Surgical treatment of ependymal glioma of spinal cord, 997
- Adolescence, kyphosis in,** 717
- Adrenals:** See Suprarenals
- Anesthesia, spinal,** 1081
- Angioneuroma:** tumor of neuromyo-arterial glomus; report of cases, 911
- Arpelt, A. A.:** Effect of jejunal feeding on gastric acidity, 875
- Appendicitis, acute, in children,** 346  
 acute; mesenteric lymphadenitis simulating acute appendicitis; quantitative study of size of normal mesenteric lymph nodes, 492  
 Schilling hemogram in, 235
- Arteries, relation to roots of nerves in posterior cranial fossa in man,** 336
- Arthritis, gonococcal, characteristics of synovial fluid in,** 721  
 gonococcus complement-fixation test in blood and synovial fluid of patients with arthritis, 720  
 treatment of acute infective arthritis of knee joint, 718
- Atrophy, muscular, experimental,** 729
- Bacteria:** See also Gonococcus; Streptococcus; etc.  
 significance of anaerobic organisms in peritonitis due to liver autolysis; bacteriologic study of peritoneal exudates, 371
- Bardenheuer-Picque resection, treatment of pyogenic osteomyelitis of sacro-iliac joint by Bardenheuer-Picque resection, modified by Orr method,** 173
- Bargen, J. A.:** Chronic ulcerative colitis with associated carcinoma; progress in management, 854
- Barr, J. S.:** Fifty-fifth report of progress in orthopedic surgery, 171  
 Fifty-sixth report of progress in orthopedic surgery, 716
- Bennett, G. E.:** Tuberculosis of diaphysis, 563
- Berec, M.:** Staphylococcal empyema and pyopneumothorax; pathogenesis, pathology, symptoms and treatment, 543
- Bile, combined and separate effects of bile, pancreatic secretion and trauma in experimental peptic ulcer,** 833
- Biliary Tract:** See also Gallbladder; Liver  
 bronchobiliary fistula, 635
- McGard, J. D.:** Osteogenesis; experimental study, 748
- Bladder:** See also Urinary Tract  
 calculus, 903  
 diagnosis of neurogenic lesions of urinary bladder by cystometry: appraisal of method based on experimentation with animals, 936  
 ectrophy, 901  
 foreign bodies, 902  
 influence of transplants on healing of defects in bone, 729
- Bladder—Continued**  
 surgery; presacral sympathectomy, 1082  
 tumors, 900  
 vesical pressure, 906
- Blood chemistry, effect of suction with nasal catheter on, report of case,** 1040  
 gonococcus complement-fixation test in blood and synovial fluid of patients with arthritis, 720
- Boggs, R.:** Peritoneal drainage; resistance of sinus tract to infection, 1032
- Bones, appearance of bone formation about elbow joint,** 723  
 atrophy; posttraumatic acute bone atrophy (Sudeck's atrophy), 173  
 calcification; decalcification and ossification, 723  
 changes in Hodgkin's granuloma, 722  
 changes in leukemias, 639  
 defects, influence of bladder transplants on healing of, 729  
 echinococcus disease in, roentgenologic characteristics, 172  
 grafts, small, 177  
 growth; effect of low calcium content on osteogenesis and healing of fractures, 177  
 growth of connective and osseous tissues in presence of certain minerals, 728  
 growth; osteogenesis, experimental study, 748  
 influence of venous stasis on heterotopic formation of bone, 729  
 lymphosarcoma, 722  
 osseous system of new-born, 177  
 Softening: See Osteomalacia  
 suppurative infections of bones and joints in infancy, 719  
 surgery, absorbable metallic material in, 176  
 transplantation of bone with reference to effect of decalcification, experimental, 178  
 transplanted; experimental studies of reparative costal chondrogenesis and transplanted bone, 178  
 transplants, study of, 728  
 tuberculosis, experimental, of bones and joints in rabbits, 178  
 tuberculosis of diaphysis, report of case, 563  
 tumors, 171  
 tumors; benign giant cell, 172
- Brain, abscess as complication in epithelioma following avulsion of scalp, report of case,** 266  
 abscess, otogenous, of parietal lobe; review of literature and report of 6 cases, 930  
 relation of arteries to roots of nerves in posterior cranial fossa in man, 336
- Breast, cancer; postoperative prognosis; results after from 7 to 20 years in series of cases studied with reference to rapidity of preoperative growth,** 629
- Bronchus; bronchobiliary fistula,** 635
- Burns, E. L.:** Epithelioma following avulsion of scalp, report of case, 266
- Buttock, gangrene of buttock, perineum and scrotum due to Endamoeba histolytica, report of case,** 980
- Calcification, decalcification and ossification,** 723  
 Calcium metabolism, pathologic fractures of spine associated with disorders of, 726
- Callus:** See under Fractures
- Calvé-Legg-Perthes' Disease:** See Osteochondritis deformans juvenilis
- Cancer:** See Tumors; and under names of organs and regions, as Breast, cancer; Check, cancer; Colon, cancer; Mouth, cancer; etc.
- Cannon, P. H.:** Effects of local immunization on development of experimental abscesses of lung, 243
- Cantarow, A.:** Hepatic function; effect of cholecystectomy on hepatic function, 865
- Carlson, H. A.:** Schilling hemogram in appendicitis, 325

# INDEX TO VOLUME 30

- Carlson, H. E.: Effect of enemas on intestinal motility, 881  
 Penetration of moist heat applied to abdomen and its effect on intestinal movements, 1036  
 Cartilage formation, experimental studies of comparative costal chondrogenesis and transplanted bone, 178  
 Catheter, suction with nasal catheter; its effect on blood chemistry, report of case, 1040  
 Cave, E. F.: Fifty-fifth report of progress in orthopedic surgery, 171  
 Fifty-sixth report of progress in orthopedic surgery, 716  
 Cheek, cancer of buccal mucosa; study of 99 cases with results of treatment at end of 5 years, 731  
 Cholecystectomy: See Gallbladder, excision  
 Cholecystogastrostomy: See under Gallbladder, surgery  
 Chondrogenesis: See Cartilage formation  
 Clawfoot: See Foot, deformities  
 Clutton's joints; symmetrical serous synovitis, 721  
 Cole, W. H.: Lymphogranuloma inguinale; its relation to stricture of rectum, 820  
 Colitis, chronic ulcerative, with associated carcinoma; progress in management, 854  
 Colles Fracture: See Radius, fractures  
 Colon, cancer; chronic ulcerative colitis with associated carcinoma; progress in management, 854  
 Comando, H. N.: Primary isolated lymphogranulomatosis of stomach, report of case, 228  
 Copeland, M. M.: Changes of bones in leukemias, 639  
 Courville, C. B.: Orogenous abscess of parietal lobe; review of literature and report of 6 cases, 930  
 Coxa Plana: See Osteochondritis deformans juvenilis  
 Vara: See Hip Joint  
 Craver, L. F.: Changes of bones in leukemias, 639  
 Cuthbert, F. P.: Effect of suprarenal denervation and splanchnic section on sugar tolerance of dogs, 151  
 Cutler, M.: Lymphosarcoma, clinical, pathologic and radiotherapeutic study with report of 30 cases, 405  
 Cystometry, diagnosis of neurogenic lesions of urinary bladder by cystometry; appraisal of method based on experimentation with animals, 956  
 Cystostomy: See Bladder, surgery  
 Cysts: See under names of organs and regions, as Knee, cysts; Tibia, cysts; etc.  
 Deformities: See Abnormalities  
 Dennis, W.: Primary sarcoma of duodenum, report of case, 875  
 de Takáts, G.: Effect of suprarenal denervation and splanchnic section on sugar tolerance of dogs, 151  
 Dextrose, massive intravenous injections, experimental study, 199  
 tolerance, effect of suprarenal denervation and splanchnic section on sugar tolerance of dogs, 151  
 Dixon, C. F.: Chronic ulcerative colitis with associated carcinoma; progress in management, 854  
 Drinker Respirator: See Respiration, artificial  
 Drury, R. B.: Congenital absence of penis, 236  
 Dry, T. J.: Differentiation of benign and malignant gastric ulcers; unreliability of diagnostic criteria, 702  
 Duodenum, primary sarcoma of; report of case, 675  
 Ulcer: See Peptic Ulcer  
 Ear infection, therapeutic use of concentrated streptococcus serum of New York State Department of Health in patients with infections of ear, nose and throat, 1  
 Echinococcosis, roentgenologic characteristics of echinococcus disease in bone, 172  
 Elbow, appearance of bone formation about elbow joint, 723  
 Embolism, pulmonary, and continuous intravenous injections, 685, 908  
 Empyema, staphylococcal empyema and pyopneumothorax; pathogenesis, pathology, symptoms and treatment, 543  
 Endamoeba histolytica; gangrene of buttock, perineum and scrotum due to; report of case, 980  
 Enemas, effect on intestinal motility, 881  
 Ependyma, surgical treatment of ependymal glioma of spinal cord, 997  
 Epilepsy secondary to head injury, 783  
 Epiphyses; epiphyseal separation of long bones, 727  
 lumbar vertebral epiphysitis, 991  
 slipping of proximal femoral epiphysis; therapeutic results in 101 cases, 607  
 Epithelioma following avulsion of scalp, report of case, 266  
 Ewing Tumors: See under Tumors  
 Fabella: See Sesamoid bone  
 Femur: See also Hip Joint  
 operative lengthening of, 725  
 slipping of proximal femoral epiphysis; therapeutic results in 101 cases, 607  
 Fibroma of Morgagni's hydatid, 1072  
 Finger; tumors of neuromyo-arterial glomus; report of case, 911  
 Fistula, bronchobiliary, 635  
 vesicovaginal, 905  
 Foot, deformities; etiology and treatment of clawfoot, report of results in 102 feet treated by anterior tarsal resection, 179  
 habitual adduction and supination distortions, 724  
 Foster, J. M., Jr.: Primary sarcoma of duodenum; report of case, 675  
 Fractures: See also under names of bones, as Radius, fracture; Spine, fracture; etc.  
 absorbable metallic material in bone surgery, 176  
 Colles: See under Radius  
 compound, studies of 236 cases, 725  
 effect of low calcium content on osteogenesis and healing of fractures, 177  
 inadequate immobilization and nonunion, 727  
 Freiberg, J. A.: Fifty-fifth report of progress in orthopedic surgery, 171  
 Fifty-sixth report of progress in orthopedic surgery, 716  
 French, R. W.: Bronchobiliary fistula, 635  
 Gallbladder: See also Bile; Biliary Tract  
 excision; effect of cholecystectomy on hepatic function, 865  
 surgery; cholecystogastrostomy and hepatitis, experimental study, 449  
 Gangrene of buttock, perineum and scrotum due to Endamoeba histolytica, report of case, 980  
 Gartner, E.: Hepatic function; effect of cholecystectomy on hepatic function, 865  
 Gas, alveolar, rate of absorption in relation to hyperventilation, 625  
 Gastric Juice: See Stomach, secretion  
 Genito-urinary tract, infection, 1084  
 Gentile, A.: Cholecystogastrostomy and hepatitis, experimental study, 449  
 Glaser, M. A.: Epilepsy secondary to head injury, 783  
 Glioma, ependymal, of spinal cord, surgical treatment of, 997  
 Glomus, tumor of neuromyo-arterial glomus; report of cases, 911  
 Glucose: See Dextrose  
 Gnathostomiasis, medial cleft of lower lip and mandible, cleft sternum and absence of basihyoid; report of case, 647  
 Gonococcus, characteristics of synovial fluid in gonococcal arthritis, 721  
 complement-fixation test in blood and synovial fluid of patients with arthritis, 720  
 Goodwin, A. M.: Effect of pneumothorax and oleothorax on histologic structure of thyroid, 667

# INDEX TO VOLUME 30

- Graves, A. M.: Combined and separate effects of bile, pancreatic secretion and trauma in experimental peptic ulcer, 833
- Growth, congenital deformities and disturbances of growth, 716
- Gutierrez, R.: Review of urologic surgery, 884, 1058
- Hansa, W. R.: Congenital absence of sacrum, 657
- Hand, synovial sheaths and fascial spaces, 172
- Harper, F. R.: Development and treatment of peptic ulcer; experimental study, 394
- Head injury, epilepsy secondary to, 783
- Heat, penetration of moist heat applied to abdomen and its effect on intestinal movements, 1036
- Henderson, F. F.: Acute pancreatitis, 1049
- Hepatitis: See under Liver
- Hepler, A. B.: Review of urologic surgery, 884, 1058
- Herrmann, L. G.: Experimental studies on pulmonary suppuration, 476
- Hershey, J. H.: Diagnosis of neurogenic lesions of urinary bladder by cystometry; appraisal of method based on experimentation with animals, 956
- Hip Joint: See also Femur  
arthroplasties, end-results, 174  
congenital coxa vara, 62
- Histamine, gastric secretion; achlorhydria following partial gastrectomy for ulcer; studies with histamine and transplanted gastric pouch, 162
- Hodgkin's Disease: See Lymphogranuloma
- Horsley, J. S.: Continuous intravenous injection, 908
- Humerus, fractures of surgical neck of humerus, reduction of, 175  
fractures of upper end, treatment of, 174
- Hydatid Cyst: See Echinococcosis
- Hydatid of Morgagni: See under Testicles
- Hydronephrosis, 884
- Hyperventilation: See Respiration, hyperpnea
- Ilium, osteomyelitis of, 718
- Infants, osseous system of new-born, 177
- Infection, relationship to postoperative pulmonary complications, 14
- Injections, intravenous; experimental pulmonary embolism associated with venoclysis, 685, 908  
intravenous, massive, experimental study, 199
- Intestines: See also Colon; Duodenum; Rectum  
melanosis coli; its clinical significance, 374  
motility, effect of enemas on, 881  
penetration of moist heat applied to abdomen and its effect on intestinal movements, 1036  
suction with nasal catheter; its effect on blood chemistry; report of case, 1040  
uretero-intestinal anastomosis, 899
- Islands of Langerhans: See under Pancreas
- Jaws, median cleft of lower lip and mandible, cleft sternum and absence of basihyoid; report of case, 647
- Jejunal feeding, effect on gastric acidity, 875
- Ulcer: See Peptic Ulcer
- Joints, suppurative infections of bones and joints in infancy, 719  
tuberculosis; functional test of reticulo-endothelial system with congo red for qualitative diagnosis of osteo-articular tuberculosis, 720  
tuberculosis of bones and joints in rabbits, experimental, 178
- Jones, H. A.: Tuberculosis of diaphysis, 563
- Jordan, H. E.: Median cleft of lower lip and mandible, cleft sternum and absence of basihyoid; report of case, 647
- Judd, E. S.: Review of urologic surgery, 884, 1058
- Kidneys: See also Hydronephrosis  
calculi, 886  
carcinoma, 888  
decapsulation, 892  
function, 894
- Kidneys—Continued  
horseshoe, 889  
ptosis; nephropexy, 894  
tumors, 886  
tumors; preoperative irradiation of clinical and pathologic study, 35
- King, E. S. A.: Acute pancreatitis, 1019
- Klein, E.: Gastric secretion; achlorhydria following partial gastrectomy for ulcer; studies with histamine and transplanted gastric pouch, 162
- Gastric secretion; action of pilocarpine on secretions of transplanted gastric pouch without Auerbach's plexus, 277
- Kleinberg, S.: Lumbar vertebral epiphysitis, 991  
Senile osteomalacia, report of case, 30
- Kling, D. H.: Hemorrhagic villous synovitis of knee joint due to xanthoma, report of case, 52
- Klippel-Feil Syndrome: See Spine, abnormalities
- Knee, acute infective arthritis, treatment, 718  
cysts of external cartilage with erosion of head of tibia, 723  
fabella (sesamoid in lateral head of gastrocnemius), 777  
hemorrhagic villous synovitis of knee joint due to xanthoma, report of case, 52  
injuries to crucial ligaments, 805  
syphilis; symmetrical serous synovitis (Clutton's joints), 721
- Kuhns, J. G.: Fifty-fifth report of progress in orthopedic surgery, 171  
Fifty-sixth report of progress in orthopedic surgery, 716
- Kyphosis: See Spine, curvature
- Larvae: See Maggots
- Legg's Disease: See Osteochondritis deformans juvenilis
- Lemmer, K. E.: Rate of absorption of alveolar gases in relation to hyperventilation, 625
- Leukemia, changes of bones in, 639
- Ligaments, Crucial: See Knee
- Lips, median cleft of lower lip and mandible, cleft sternum and absence of basihyoid; report of case, 647
- Liver: See also Biliary Tract  
autolysis, significance of anaerobic organisms in peritonitis due to bacteriologic study of peritoneal exudates, 371  
cholecystogastrostomy and hepatitis, experimental study, 449  
function; effect of cholecystectomy on, 865
- Longacre, J. J.: Experimental studies on pulmonary suppuration, 476
- Lung, abscesses, experimental, effects of local immunization on development of, 243  
rate of absorption of alveolar gases in relation to hyperventilation, 625  
relationship of infection to postoperative pulmonary complications, 14  
suppuration, experimental studies, 476
- Tuberculosis: See Tuberculosis
- Lymph nodes, mesenteric lymphadenitis simulating acute appendicitis; quantitative study of size of normal mesenteric lymph nodes, 492
- Lymphogranuloma, bone changes in Hodgkin's granuloma, 722  
linguale, its relation to stricture of rectum, 820  
primary isolated lymphogranulomatosis of stomach, report of case, 228
- Lymphosarcoma, clinical, pathologic and radiotherapeutic study with report of 30 cases, 405  
in bone, 722
- McCaughan, J. M.: Diagnosis of neurogenic lesions of urinary bladder by cystometry; appraisal of method based on experimentation with animals, 956
- McKillop, A. N.: Relation of arteries to roots of nerves in posterior cranial fossa in man, 336



# INDEX TO VOLUME 30

- MacNeal, W. J.: Therapeutic use of concentrated streptococcus serum of New York State Department of Health in patients with infections of ear, nose and throat, 1
- Therapeutic use of concentrated streptococcus serum of New York State Department of Health; infected wounds, 357
- McWhorter, G. L.: Clinical use of plastic pyloroplasty in chronic duodenal ulcer, 528
- Maggots, adequacy of nutritional retardation in culture of sterile maggots for surgical use, 1024
- use of low temperatures in culture and transportation of surgical maggots, 1015
- Mahorner, H. R.: Histologic effects of intravenous sclerosing solutions on subcutaneous tissues, 573
- Mammary Gland: See Breast
- Mandible: See Jaws
- Martin, H. E.: Cancer of cheek (buccal mucosa); study of 99 cases with results of treatment at end of 5 years, 731
- Significance of anaerobic organisms in peritonitis due to liver autolysis; bacteriologic study of peritoneal exudates, 371
- Mayer, L.: Tumor of neuromyo-arterial glomus; report of cases, 911
- Mead, C. H.: Mesenteric lymphadenitis simulating acute appendicitis; quantitative study of size of normal mesenteric lymph nodes, 492
- Melanin, pigmentation; melanosis coli; clinical significance, 974
- Melanosis: See Melanin, pigmentation
- Meleney, F. L.: Gangrene of buttock, perineum and scrotum due to *Endamoeba histolytica*; report of case, 980
- Meleney, H. E.: Gangrene of buttock, perineum and scrotum due to *Endamoeba histolytica*; report of case, 980
- Meitzer, S.: Effect of pneumothorax and oleothorax on histologic structure of thyroid, 667
- Meningitis as complication in epithelioma following avulsion of scalp, report of case, 266
- Mesentery; mesenteric lymphadenitis simulating acute appendicitis; quantitative study of size of normal mesenteric lymph nodes, 492
- Metallic material, absorbable, in bone surgery, 176
- Milch, H.: Injuries to crucial ligaments, 805
- Milgram, J. E.: Fifty-fifth report of progress in orthopedic surgery, 171
- Fifty-sixth report of progress in orthopedic surgery, 176
- Morton, C. B.: Median cleft of lower lip and mandible, cleft sternum and absence of basihyoid; report of case, 647
- Meuth, cancer of cheek (buccal mucosa), study of 99 cases with results at end of 5 years, 731
- Muscles, Atrophy: See Atrophy, muscular
- common syndrome of rupture, dislocation and elongation of long head of biceps brachii muscle, 723
- gastrocnemius; fabella (sesamoid in lateral head of gastrocnemius), 777
- skeletal muscle sarcoma, 722
- Nails, tumors of neuromyo-arterial glomus, 911
- Neck, congenital webbed neck, 716
- Nephropexy: See Kidneys, ptosis
- Nerves, relation of arteries to roots of nerves in posterior cranial fossa in man, 336
- splanchnic; effect of suprarenal denervation and splanchnic section on sugar tolerance of dogs, 151
- Nervous System, gastric secretion: action of pilocarpine on secretions of transplanted gastric pouch without Auerbach's plexus, 277
- surgery; presacral sympathectomy, 1082
- Neuhof, H.: Staphylococcal empyema and pyopneumothorax; pathogenesis, pathology, symptoms and treatment, 543
- Neurofibroma of ureter, report of case with operation and recovery, 442
- New-Born: See Infants
- New York State Department of Health, therapeutic use of concentrated streptococcus serum of, in infected wounds, 357
- State Department of Health, therapeutic use of concentrated streptococcus serum in patients with infections of ear, nose and throat, 1
- Nilsen, J. M.: Otogenous abscess of parietal lobe; review of literature and report of 6 cases, 930
- Northrop, R. F.: Suction with nasal catheter; its effect on blood chemistry; report of case, 1040
- Nose infection, therapeutic, use of concentrated streptococcus serum of New York State Department of Health in patients with infections of ear, nose and throat, 1
- Ochsner, A.: Histologic effects of intravenous sclerosing solutions on subcutaneous tissues, 573
- O'Connor, V. J.: Review of urologic surgery, 884, 1058
- Oleothorax, effect of pneumothorax and oleothorax on histologic structure of thyroid, 667
- Orr, T. G.: Effect of enemas on intestinal motility, 881
- Penetration of moist heat applied to abdomen and its effect on intestinal movements, 1036
- Orr method of treatment of pyogenic osteomyelitis of sacro-iliac joint by modification of Bardenheuer-Picque resection, 173
- Orthopedic surgery, fifty-fifth report of progress in, 171
- fifty-sixth report of progress in, 176
- Ossification, calcification and decalcification, 723
- Osteochondritis deformans juvenilis; end-results of coxa plana as related to treatment, 717
- deformans juvenilis; treatment of Legg-Calvé-Perthes disease without weight bearing, 717
- dissecans; intra-articular osteocartilaginous loose bodies, 173
- Osteogenesis: See Bones, growth
- Osteomalacia, senile, report of case, 30
- Osteomyelitis of ilium, 718
- treatment of pyogenic osteomyelitis of sacro-iliac joint by Bardenheuer-Picque resection, modified by Orr method, 173
- Pancreas, carcinoma of body and tail of, 584
- secretion; combined and separate effects of bile, pancreatic secretion and trauma in experimental peptic ulcer, 833
- Pancreatitis, acute, 1049
- Patella, fractures, 727
- Patterson, G. H.: Surgical treatment of ependymal glioma of spinal cord, 997
- Penis, absence, congenital, 236
- Peptic Ulcer, clinical use of plastic pyloroplasty in chronic duodenal ulcer, 528
- development and treatment, experimental study, 394
- differentiation of benign and malignant gastric ulcers; unreliability of diagnostic criteria, 702
- effect of jejunal feeding on gastric acidity, 875
- experimental, combined and separate effects of bile, pancreatic secretion and trauma in, 833
- reactions of contents of jejunum and experimental production of peptic ulcer, 557
- Perineum, gangrene of buttock, perineum and scrotum due to *Endamoeba histolytica*; report of case, 980
- Peritoneum, Drainage: See Abdomen, drainage
- significance of anaerobic organisms in peritonitis due to liver autolysis; bacteriologic study of peritoneal exudates, 371
- study of peritoneal exudates, 371
- Penitonsitis, penetration of moist heat applied to abdomen and its effect on intestinal movements, 1036
- significance of anaerobic organisms in, 371
- Perthes' Disease: See Osteochondritis deformans juvenilis

# INDEX TO VOLUME 30

- Fluegger, O. H.: Cancer of cheek (buccal mucosa); study of 99 cases with results of treatment at end of 5 years, 731
- Phloerapine, action on secretions of transplanted gastric pouch without Auerbach's plexus, 277
- Pituitary Body, Irradiation in tumors, report of 23 cases, 102
- Pneumaturia, 1082
- Pneumothorax, effect of pneumothorax and oleothorax on histologic structure of thyroid, 667
- Poliomyelitis, mixed intra-articular and extra-articular arthrodesis of shoulder in, 724 treated with Drinker respirator; analysis of 88 cases and 68 control cases, 719
- Pomeranz, M. M.: Fabella (sesamoid in lateral head of gastrocnemius), 777
- Slipping of proximal femoral epiphysis; therapeutic results in 101 cases, 607
- Prey, D.: Primary sarcoma of duodenum, 675
- Prostate, calculi, 1058
- carcinoma, 1068
- resection, 1061
- sarcoma, 1068
- Puberty; See Adolescence
- Pyelonephritis, 895
- Pyloroejunostomy; See under Peptic Ulcer
- Pyopneumothorax, staphylococci empyema and pyopneumothorax; pathogenesis, pathology, symptoms and treatment, 543
- Radius, fractures of radius and ulna, new anatomic method of treatment, 175
- Rainey, W.: Lymphogranuloma inguinale; its relation to stricture of rectum, 820
- Raisman, V.: Tumor of neuromyo-arterial glomus; report of cases, 911
- Rand, C. W.: Irradiation in treatment of tumors of pituitary, report of 23 cases, 103
- Ransom, H. K.: Carcinoma of body and tail of pancreas, 584
- Ravich, A.: Neurofibroma of ureter; report of case with operation and recovery, 442
- Rectum, cancer; chronic ulcerative colitis with associated carcinoma; progress in management, 854
- stricture; lymphogranuloma inguinale and its relation to stricture of rectum, 820
- Reeves, J. R.: Significance of anaerobic organisms in peritonitis due to liver autolysis; bacteriologic study of peritoneal exudates, 371
- Respiration, artificial; Drinker respirator in poliomyelitis, 719
- hyperpnea; rate of absorption of alveolar gases in relation to hyperventilation, 625
- Respiratory tract infections, therapeutic use of concentrated streptococcus serum of New York State Department of Health, 1
- Reticulo-Endothelial System, functional test with congo red for qualitative diagnosis of osteo-articular tuberculosis, 720
- Ribs, experimental studies of reparative costal chondrogenesis and transplanted bone, 178
- Riccioli, G.: Hepatic function; effect of cholecystectomy on hepatic function, 865
- Rivers, A. B.: Differentiation of benign and malignant gastric ulcers; unreliability of diagnostic criteria, 702
- Roberts, S. M.: Fifty-fifth report of progress in orthopedic surgery, 171
- Fifty-sixth report of progress in orthopedic surgery, 116
- Rogers, W. A.: Treatment of fractures of vertebral bodies uncomplicated by lesions of cord, 284
- Rosenstine, E. A.: Rate of absorption of alveolar gases in relation to hyperventilation, 625
- Rumold, M. J.: Experimental pulmonary embolism associated with venoclysis, 685; reply by J. S. Horsley, 908
- Sacro-iliac joint, treatment of prostatic osteomyelitis of sacro-iliac joint by Bardenheuer-Picque resection, modified by Orr method, 173
- Sacrum, absence of, congenital, 657
- Sarcoma, primary, of duodenum, report of case, 675
- prostate, 1068
- skeletal muscle sarcoma, 722
- Sashin, D.: Hemorrhagic villous synovitis of knee joint due to xanthoma, report of case, 52
- Saunders, J. T.: Etiology and treatment of clawfoot; report of results in 102 feet treated by anterior tarsal resection, 179
- Scalp, avulsion, epithelioma following, report of case, 266
- Schilling hemogram in appendicitis, 325
- Scholl, A. J.: Review of urologic surgery, 884, 1058
- Schwarzell, R. H.: Congenital absence of penis, 236
- Sclerosing solutions, intravenous, histologic effects on subcutaneous tissues, 573
- Scoliosis; See Spine, curvature
- Scrotum, gangrene of buttock, perineum and scrotum due to Endamoeba histolytica; report of case, 980
- Seminal vesicle, carcinoma, 1074
- Sesamoid bone, fabella (sesamoid in lateral head of gastrocnemius), 777
- Shafer, F. P.: Epilepsy secondary to head injury, 783
- Shambaugh, P.: Peritoneal drainage; resistance of sinus tract to infection, 1032
- Sheplar, A. E.: Therapeutic use of concentrated streptococcus serum of New York State Department of Health in patients with infections of ear, nose and throat, 1
- Therapeutic use of concentrated streptococcus serum of New York State Department of Health; infected wounds, 357
- Shoulder, mixed intra-articular and extra-articular arthrodesis of shoulder in poliomyelitis, 724
- reductions of old and irreducible dislocations, 725
- roentgenography; improved technic for examination of shoulder, 172
- Simmons, S. W.: Adequacy of nutritional retardation in culture of sterile maggots for surgical use, 1024
- Use of low temperatures in culture and transportation of surgical maggots, 1015
- Simon, S. M.: Fabella (sesamoid in lateral head of gastrocnemius), 777
- Sloane, M. F.: Slipping of proximal femoral epiphysis; therapeutic results in 101 cases, 607
- Sodium chloride, massive intravenous injections, experimental study, 199
- Spence, M. J.: Therapeutic use of concentrated streptococcus serum of New York State Department of Health in patients with infections of ear, nose and throat, 1
- Therapeutic use of concentrated streptococcus serum of New York State Department of Health; infected wounds, 357
- Spermatocoele, vaso-orchidostomy with interposed spermatocele; procedure for treatment of sterility, 967
- Spinal Cord, ependymal glioma, surgical treatment, 997
- lesions causing neurogenic lesions of urinary bladder, diagnosis by cystometry; appraisal of method based on experimentation with animals, 956
- Spine, abnormalities; Klippel-Feil syndrome: congenital webbed neck, 716
- curvature; adolescent kyphosis, 717
- fractures; compression fractures of vertebral bodies, 726
- fractures of vertebral bodies uncomplicated by lesions of cord, treatment of, 284
- fractures, pathologic, associated with disorders of calcium metabolism, 726
- lumbar vertebral epiphysitis, 991
- Stanton, E. M.: Postoperative prognosis in cancer of breast; results after from 7 to 20 years in series of cases studied with reference to rapidity of preoperative growth, 629

# INDEX TO VOLUME 30

- Staphylococci; staphylococcal empyema and pyopneumothorax: pathogenesis, pathology, symptoms and treatment, 543
- Steel, B. F.: Relationship of infection to postoperative pulmonary complications, 14
- Stephenson, E.: Effect of pneumothorax and oleothorax on histologic structure of thyroid, 667
- Sterility, vaso-orchidostomy with interposed spermatocele; procedure for treatment of sterility, 967
- Sternum, median cleft of lower lip and mandible, cleft sternum and absence of biliary; report of case, 647
- Stirling, R. I.: Fifty-fifth report of progress in orthopedic surgery, 171  
Fifty-sixth report of progress in orthopedic surgery, 716
- Stomach, acidity; effect of jejunal feeding on, 875  
cancer, differentiation of benign and malignant gastric ulcers; unreliability of diagnostic criteria, 702  
primary isolated lymphogranulomatosis, report of case, 228  
secretion; achlorhydria following partial gastrectomy for ulcer; studies with histamine and transplanted gastric pouch, 162  
secretion; action of pilocarpine on secretions of transplanted gastric pouch without Auerbach's plexus, 277  
secretion; effect of jejunal feeding on gastric acidity, 875
- Ulcer: See Peptic Ulcer
- Stone, C. S., Jr.: Acute appendicitis in children, 346
- Streptococcus serum, therapeutic use of concentrated streptococcus serum of New York State Department of Health in infected wounds, 357  
serum, therapeutic use of concentrated streptococcus serum of New York State Department of Health in patients with infections of ear, nose and throat, 1
- Sudek's Atrophy: See Bones, atrophy
- Sugar Tolerance: See Dextrose tolerance
- Suprarenals, innervation; effect of suprarenal denervation and splanchnic section on sugar tolerance of dogs, 151
- Surgery, blood in; Schilling hemogram in appendicitis, 325  
postoperative complications; relationship of infection to postoperative pulmonary complications, 14  
postoperative treatment; suction with nasal catheter: its effect on blood chemistry, 1040
- Susnow, D. A.: Melanosis coli; its clinical significance, 974
- Sutcliffe, W. D.: Relationship of infection to postoperative pulmonary complications, 14
- Sutro, C. J.: Fabcilla (sesamoid in lateral head of gastrocnemius), 777
- Sympathectomy, presacral, 1082
- Synovial fluid, characteristics in gonococcal arthritis, 721  
gonococcus complement-fixation test in blood and synovial fluid of patients with arthritis, 720
- Synovitis, hemorrhagic villous synovitis of knee joint due to xanthoma, report of case, 52
- Taylor, R. G.: Irradiation in treatment of tumors of pituitary, report of 23 cases, 103
- Testicles, tumor, 1072  
tumor (fibroma) of Morgagni's hydatid, 1072  
undescended, 1070  
vaso-orchidostomy with interposed spermatocele; procedure for treatment of sterility, 967
- Throat infections, therapeutic use of concentrated streptococcus serum of New York State Department of Health in patients with infections of ear, nose and throat, 1
- Thrombosis of renal veins, 891
- Thyroids, effect of pneumothorax and oleothorax on histologic structure, 667
- Tibia, compound fractures, treatment of, 176  
cysts of external cartilage of knee with erosion of head of tibia, 723  
fracture of tibial spine, 175
- Tissues, subcutaneous, histologic effects of intravenous sclerosing solutions on, 573
- Torticollis, congenital, 716  
operative treatment, results of, 174
- Trochanter: See Femur
- Trusler, H. M.: Significance of anaerobic organisms in peritonitis due to liver autolysis; bacteriologic study of peritoneal exudates, 371
- Tuberculin, effects of tuberculinoprotein on course of experimental tuberculosis in rabbits and guinea-pigs, 730
- Tuberculosis: See also Bones, tuberculosis; Joints, tuberculosis; etc.  
experimental; effects of tuberculinoprotein in rabbits and guinea-pigs, 730  
functional test of reticulo-endothelial system with congo red for qualitative diagnosis of osteo-articular tuberculosis, 720  
surgical, treatment by climate and sunlight during 47 years, 720
- Tumors: See also Epithelioma; Sarcoma; etc., and under names of organs and regions  
Ewing's, review of, 171  
of neuromyo-arterial glomus; report of cases, 911  
radiosensitivity, 171
- Tuttle, W. M.: Effects of local immunization on development of experimental abscesses of lung, 243
- Ulna, fractures of radius and ulna, new anatomic method of treatment, 175
- Ureter, neurofibroma, report of case with operation and recovery, 442  
tumors, 897  
uretero-intestinal anastomosis, 899
- Urethra, trauma, 1069
- Urinary Tract, calculus, 1075  
roentgenography (urography), 1079
- Urography: See Urinary Tract, roentgenography
- Urologic surgery, review of, 884, 1058
- Varicose veins, histologic effects of intravenous sclerosing solutions on subcutaneous tissues, 573
- Vaso-orchidostomy with interposed spermatocele; procedure for treatment of sterility, 967
- Veins: See also Embolism; Thrombosis; etc.  
influence of venous stasis on heterotopic formation of bone, 729
- Venoclysis: See Injections, intravenous
- Veinbrugge, J.: Review of urologic surgery, 884, 1058
- Vertebra: See Spine
- Warthen, H. J.: Massive intravenous injections, experimental study, 199
- Watt, J. C.: Relation of arteries to roots of nerves in posterior cranial fossa in man, 336
- Wharton, L. R.: Preoperative irradiation of massive tumors of kidney, clinical and pathologic study, 35
- Wilder, L.: Schilling hemogram in appendicitis, 325
- Wilhelm, S. F.: Vaso-orchidostomy with interposed spermatocele; procedure for treatment of sterility, 967
- Wounds, infected, therapeutic use of concentrated streptococcus serum of New York State Department of Health in, 357
- Wry-Neck: See Torticollis
- Wu, P. P. T.: Reactions of contents of jejunum and experimental production of peptic ulcer, 557
- Xanthoma, hemorrhagic villous synovitis of knee joint due to, report of case, 52
- Zadek, I.: Congenital coxa vara, 62
- Zobel, A. J.: Melanosis coli; its clinical significance, 974



ried out. All the patients were in good clinical condition before and during operation, and there were no fatalities.

The serum bilirubin was determined by the quantitative van den Bergh procedure as modified by Thannhauser and Andersen. As stated in a previous report,<sup>1</sup> the normal range of serum bilirubin, according to our experience, is from 0.1 to 1 mg. per hundred cubic centimeters; in about 50 per cent of the persons the serum bilirubin falls below 0.5 mg.,

TABLE 1.—Data for Patients Showing No Preoperative Hyperbilirubinemia or Retention of Dye

Patient	Serum Bilirubin, Mg. per 100 Cc.		Retention of Dye, Percentage	
	Before	After	Before	After
L. F. ....	0.40	0.76	0	0
A. L. ....	0.50	0.90	0	10
A. An. ....	1.00	0.90	0	0
E. Th. ....	0.40	0.26	0	0
L. C. ....	0.62	0.86	0	0
I. B. ....	0.90	1.30	0	0
T. Y. ....	0.72	0.86	0	0
A. S. ....	0.70	1.10	0	10
E. Lc. ....	0.85	1.20	0	0
A. Ab. ....	0.80	1.20	0	10
E. Lcl. ....	0.65	0.84	0	0
J. D. ....	0.57	0.74	0	0
M. M. ....	0.60	0.90	0	10
M. G. ....	0.72	0.98	0	0
T. M. ....	0.48	0.72	0	0
H. McA. ....	0.48	0.75	0	10
J. C. ....	0.37	0.62	0	0
F. R. ....	0.92	0.90	0	20
A. M. ....	0.36	0.64	0	0
A. DeC. ....	0.60	1.20	0	10
S. S. ....	0.72	0.74	0	10
B. Z. ....	0.52	1.09	0	20
R. H. ....	0.55	0.36	0	30
M. R. ....	0.76	1.40	0	0
J. R. ....	0.52	1.10	0	25
M. K. ....	0.41	0.70	0	10
S. B. ....	0.32	0.40	0	20
A. Ca. ....	0.50	0.50	0	15
S. V. ....	0.65	0.90	0	0
L. V. ....	0.80	0.42	0	0
M. Sm. ....	0.68	0.32	0	0
C. W. ....	0.56	1.08	0	0
M. Sh. ....	0.40	0.60	0	0
M. H. ....	0.39	0.52	0	0
S. B. ....	0.35	0.65	0	0
L. C. ....	0.11	0.12	0	0
S. R. ....	0.30	0.60	0	20
C. M. ....	0.70	0.60	0	50
M. M. ....	0.43	0.23	0	0
A. K. ....	0.80	0.36	0	0
C. C. ....	0.68	0.46	0	0

and in about 95 per cent it fell below 0.8 mg. Bromsulphthalein was administered in the dosage of 2 mg. per kilogram of body weight, the degree of retention being determined at the end of thirty minutes.

Several studies were made in the majority of instances; the two figures reported here are those obtained within twenty-four hours before and twenty-four hours after cholecystectomy. No morphine was administered to any patient in this series between the time of operation and the reported postoperative observations.

1. Cantarow, A.: Hepatic Function: I. Noncalculous and Calculous Cholecystitis, Arch. Int. Med. 54:540 (Oct.) 1934.

In order to simplify the analysis of the experimental data, the patients may be divided into several groups in accordance with observations made before operation.

*Patients with No Preoperative Hyperbilirubinemia or Retention of Dye.*—There were forty-one patients who before operation showed neither hyperbilirubinemia nor retention of bromsulphalein after thirty minutes. The detailed findings are presented in table 1. A significant increase in the concentration of serum bilirubin twenty-four hours after

TABLE 2.—Data for Patients Showing Preoperative Hyperbilirubinemia or Retention of Dye

Patient	Serum Bilirubin, Mg. per 100 Cc.		Retention of Dye, Percentage	
	Before	After	Before	After
M. R. ....	2.00	1.20	10	10
R. M. ....	0.65	0.70	5	0
M. C. ....	0.90	1.40	5	10
E. F. ....	0.50	1.00	10	20
P. S. ....	0.70	0.55	5	15
M. P. ....	0.70	0.92	5	20
J. A. ....	0.80	0.62	25	60
J. M. ....	0.70	0.75	5	0
F. C. ....	2.40	0.50	0	0
E. T. ....	0.80	0.40	100	5
F. G. ....	1.20	0.50	0	10
M. L. ....	1.10	0.58	0	10
J. R. ....	1.10	2.24	0	15
T. F. ....	1.36	1.20	15	0
A. Cu. ....	0.44	2.76	5	20
L. A. ....	1.20	0.10	0	0
E. M. ....	2.24	0.63	45	5
M. L. ....	2.40	3.60	15	55
J. H. ....	0.75	0.92	5	10

TABLE 3.—Summary of Data for Patients with No Preoperative Retention of Dye

Cases	Serum Bilirubin				Retention of Dye		
	Before, Mg. per 100 Cc.	After, Mg. per 100 Cc.	Increased	Decreased	Before	After	Increased
46	0.11-2.40	0.12-2.24	27 (60%)	13 (28%)	0	0-50	19 (41%)

cholecystectomy occurred in twenty-six cases (63.4 per cent), the value being above the upper limit of normal (1 mg.) in nine instances (21.9 per cent). An abnormal degree of retention of dye (from 10 to 50 per cent) was noted twenty-four hours after operation in sixteen cases (39 per cent).

There was no apparent relation between the postoperative increase in serum bilirubin and the retention of dye. Of the sixteen patients in whom retention of dye occurred, two showed decrease in the concentration of serum bilirubin (R. H. and C. M., table 1). Furthermore, these two patients exhibited the most marked degree of retention of dye observed in this group (30 and 50 per cent). In five instances reten-